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ORGANIC PHOSPHATES OF THE BLOOD AND MINERAL METABOLISM IN DIABETIC ACIDOSIS

PRESIDENT'S ADDRESS

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CINCINNATI

In this critical period we should all like to be doing work which promises to help our country and our allies to victory. Hence it may sometimes seem futile now to be continuing some of the investigations which have seemed important during peace times. Such research quite rightly is apt to be looked on with disfavor if it is carried on in the spirit of "business as usual," with disregard for the war emergencies. But until suitable opportunities are found for work more closely identified with the war effort, there is as great a necessity as ever for the solution of all problems which concern the health of children. This evening's session will be devoted to the discussion of problems of nutrition, which assume increased importance due to the exigencies of war.[1] The program this afternoon and tomorrow[2] is devoted to subjects of perennial interest, whether in times of war or of peace.

In calling to order the fourteenth meeting of this society, I should like to express my appreciation of the honor you bestowed in electing me your president. Having been one of those who gathered in Boston in the spring of 1929 for the first meeting, I have enjoyed seeing this society since its beginning serve an increasingly useful function in the furtherance of pediatric research; and, in addition, I have seen both old and new members develop an attitude of personal affection for the organization that tells much about its success. In retrospect, I recall that during the first years, when the name was the Eastern Society for

Read at the fourteenth annual meeting of the Society for Pediatric Research, Skytop, Pa., April 29, 1942.

From the Children's Hospital Research Foundation and the Department of Pediatrics, College of Medicine, University of Cincinnati.

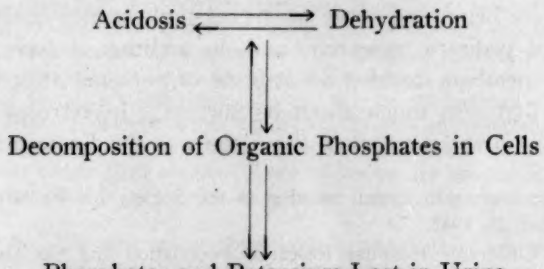
1. Symposium on Nutritional Research as Related to Children in Wartime, led by Dr. John R. Murlin, Professor of Physiology, University of Rochester, and Chairman of Committee on Food and Nutrition of the National Research Council.

2. Proceedings to be published in American Journal of Diseases of Children.

Pediatric Research, there was a suggestion of the bar sinister hovering over two or three of us who had moved out of the eastern orbit before the spring of 1929. Dr. Johnston, senior member of the council this year, also was in that category. Although, to be sure, a touch of illegitimacy could scarcely detract from our own pleasure, we did welcome a little later the removal of that bar sinister from our escutcheon by a change in the name of the society—a change made so that this suggestion could not be imputed to the others who traveled long distances to be adopted. Withal, we have had a merry family during these years, and we can justly claim of our brain children, in the language of Falstaff, that there has been much fun in their making.

Last year the custom was established that the president should deliver an address concerned, preferably, with his own work; thus it seems that my topic should be somehow connected with phosphorus. Accordingly, I have chosen to discuss the interdependence of certain phases of the mineral metabolism of the body and the metabolism of some of the organic phosphorus compounds in the blood and tissue cells.[3] In the studies to be summarized here I have enjoyed the collaboration of Dr. S. Rapoport, Mr. E. Leva and Miss Mary Wing, of the Children's Hospital Research Foundation; of Dr. I. A. Mirsky and Dr. N. Nelson, of the May Institute of the Jewish Hospital of Cincinnati; of Dr. L. Owens and Dr. J. Wright and other members of the department of medicine in the Cincinnati General Hospital. To all of these I am grateful for their generous cooperation.

I shall begin with a summary of interrelationships that have been traced between changes of organic phosphates in the blood and tissue cells and the more familiar changes of electrolytes in the extracellular fluids in diabetic acidosis and then present some of the data on which this concept is based. These interrelationships are illustrated by the following scheme which represents the interdependence of acidosis, dehydration and losses of intracellular electrolytes:



Acidosis and dehydration in the diabetic patient are mutually influenced by many interrelated factors in the disturbances which

3. For a more general summary of this subject and bibliography, see Guest, G. M., and Rapoport, S.: Organic Acid-Soluble Phosphorus Compounds of the Blood, Physiol. Rev. **21**:410-437 (July) 1941.

precede, accompany and follow the development of the acidotic state. The loss of electrolytes from the body by urinary excretion is a well recognized factor in the development of dehydration. The rapid development of severe acidosis is accompanied by excessive phosphaturia that results mainly from the decomposition of labile organic phosphates in the blood and tissue cells. The depletion of the latter substances is both a cause and an effect of functional disturbances in various phases of cellular metabolism in which those compounds are concerned; and the excessive phosphaturia is both a cause and an effect of the concomitant excessive excretion of sodium and potassium, which in turn aggravates the development of dehydration and acidosis. In the blood cells, decreases in concentration of the organic phosphates are associated with decreases in the concentration of potassium. During recovery from acidosis the restoration of a normal chemical structure of the blood involves the replacement of potassium concomitantly with resynthesis of the organic phosphates in the blood cells. Indirect evidence suggests that such changes reflect similar changes in the state of the labile stores of phosphorus and potassium in other tissue cells.

The organic phosphates, as nondiffusible anions, exert a strong influence on the distribution of the diffusible ions between the cells and the plasma. Changes in concentration of these organic phosphates are an essential part of the adjustments in the distribution of electrolytes in the blood which characterize the acidotic state. Thus, the glycolytic enzyme system, by which the organic phosphates are synthesized and decomposed, may be regarded as a principal mechanism in the maintenance of the acid-base equilibrium of the blood.

The observations which are to be cited as a basis for these premises are presented with the expectation that they will provoke more questions than they answer—and with the hope that thereby more investigations along these lines will be stimulated.

EXPERIMENTAL OBSERVATIONS

Chart 1 represents the rate of phosphorus excretion in the urine of an adult diabetic patient, E. W., an analysis of whose blood is presented in figure 5. This patient[4] had been in coma several hours

4. Studies of this patient have been presented in a different manner in earlier publications: (Guest, G. M., and Rapoport, S.: [*a*] Role of Acid-Soluble Phosphorus Compounds in Red Blood Cells in Experimental Rickets, Renal Insufficiency, Pyloric Obstruction, Gastroenteritis, Ammonium Chloride Acidosis and Diabetic Acidosis, Am. J. Dis. Child. **58**:1072-1089 [Nov.] 1939; [*b*] The Role of Diphosphoglycerate and Other Organic Acid-Soluble Phosphorus Compounds of the Red Blood Cells in the Electrolyte Equilibrium of the Blood, in Blood, Heart and Circulation, Symposium, Publication 13, American Association for the Advancement of Science, New York, Science Press, 1940, pp. 55-60).

before her admission to the hospital, when the observations and treatment were started. Treatment consisted in the immediate administration of insulin and of sodium chloride and dextrose solutions subcutaneously and intravenously. At four and one-half hours the extreme state of acidosis was corrected by the intravenous injection of sodium bicarbonate. During the first urine collection period, of four and one-half hours, the phosphorus excretion was at the rate of 163 mg. per hour; during the next six hours it dropped to 47 mg. per hour, and during the next period, of twelve hours, to only 2 mg. per hour. During seven days thereafter the phosphaturia was slight, about 1 mg. of phosphorus or less being excreted per hour. Later, during the twelfth to the fifteenth day, inclusive, the rate was between 10 and 15 mg. per hour. When correlated with the changes in the distribution of phosphorus in the blood which are to be discussed, these observations were

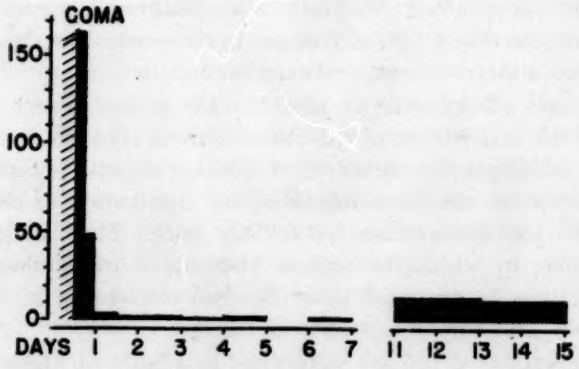


Chart 1.—Milligrams of phosphorus excreted per hour in the urine of the patient, E. W., during diabetic acidosis and recovery.

interpreted to mean that during the period of acidosis the excessive phosphaturia had exhausted the phosphorus reserves of this patient; that phosphorus was retained in the body during the period of recovery, when the organic phosphates were being resynthesized in the tissues, and that the urinary excretion of phosphorus became normal with the restoration of the phosphates to normal concentrations in the blood and tissues.

Limited amounts of phosphates are, of course, excreted in the urine under normal conditions as waste products of physiologic metabolism. An increased excretion of phosphates has been commonly regarded as a physiologic mechanism for the conservation of base in the body. It is important to note, however, that this mechanism at best is only partly successful. Severe rapidly developing acidosis is accompanied by an

excessive excretion of potassium as well as of phosphorus, and such excretion reflects a breakdown of intracellular constituents which quickly attains primary importance in the acidotic state.

Inasmuch as the distribution of phosphorus in the blood has been dealt with previously in this journal,[4a] it seems unnecessary to repeat such discussion here. It should be noted, however, that the organic acid-soluble phosphates are confined to the cells; that the diphosphoglycerate normally makes up about half of the total organic acid-soluble phosphorus, and that it is in the diphosphoglycerate fraction that there

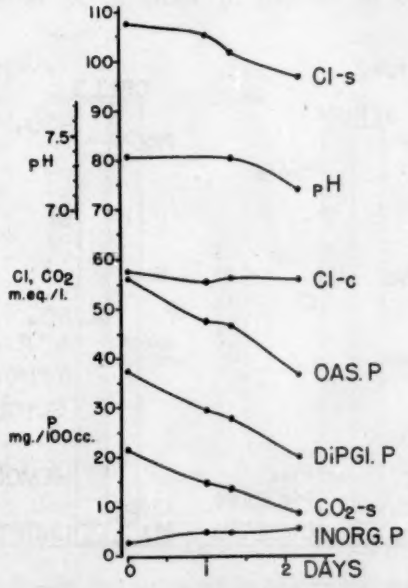


Chart 2.—Changes in the blood of a depancreatized dog during the development of acidosis following the injection of phlorhizin. *Cl—s, Cl—c* represents the chloride in the serum and cells; *OAS.P,* organic acid-soluble phosphorus in cells; *DipGl.P,* diphosphoglycerate in cells; *CO_2—s,* carbon dioxide content of the serum; *Inorg.P,* inorganic phosphorus in the whole blood.

are found the greatest changes in a variety of pathologic conditions in which the phosphorus metabolism of the body is deranged.

Chart 2 illustrates changes observed in the blood of a depancreatized dog during the development of acidosis that followed the withholding of insulin and the injection of phlorhizin. Phlorhizin was injected to deplete quickly the glycogen of the liver, thereby precipitating the rapid development of ketosis and acidosis, a technic that has been much used by Dr. Mirsky and his colleagues in their studies of carbohydrate metabolism. The concentration of organic acid-soluble phosphorus in

the blood cells decreased concurrently with the decrease of carbon dioxide in the blood serum, and the decrease of the organic acid-soluble phosphorus was almost exactly accounted for by the decrease in the diphosphoglycerate fraction. Thus one visualizes changes occurring in the blood during early stages of the development of diabetic acidosis.

Inasmuch as the diphosphoglycerate and other organic acid-soluble phosphorus compounds in the blood cells are synthesized and decomposed by the glycolytic enzymes, all changes in their concentration must be accounted for by factors which influence these enzymatic reactions. In vitro the decomposition of the phosphoric esters in the blood cells has been found to be favored by shifts in p_H of the blood toward

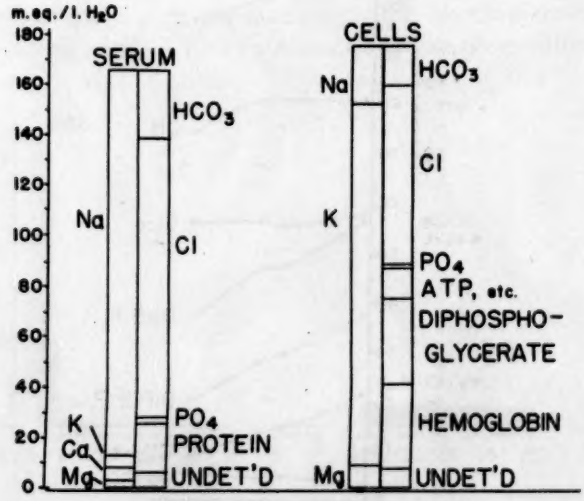


Chart 3.—Acid-base composition of the serum and cells of normal human blood. Anions: sodium, potassium, calcium, magnesium. Cations: bicarbonate, chloride, inorganic phosphorus (*PO*$_4$), adenosinetriphosphate and other organic acid-soluble phosphates (*ATP*, etc.), diphosphoglycerate, protein, hemoglobin and undetermined (*UNDET'D*) cation equivalents obtained by difference.

increased acidity, i. e. to p_H less than 7.3, and in vivo this decomposition is probably also favored by shifts in the chloride content and by other less well defined factors in the acidotic state.[5]

The next two charts are designed to show how the organic acid-soluble phosphorus compounds fit in the electrolyte composition of the blood under normal conditions and in diabetic acidosis.

5. Rapoport, S., and Guest, G. M.: The Decomposition of Diphosphoglycerate in Acidified Blood: Its Relationship to Reactions of the Glycolytic Cycle, J. Biol. Chem. **129**:781-790 (Aug.) 1939.

In chart 3 the acid-base composition of the serum and cells of normal blood is represented in the style of diagram that has been made famous by Dr. James L. Gamble, who honored this society as its first president. The concentrations of the anions and cations are expressed in milliequivalents per liter of water. It is to be remembered that the water content of the serum is about 93 per cent, but in the cells it is only 70 per cent. In the cells the concentration of the diffusible chloride and bicarbonate ions is about two-thirds that found in the serum, the difference being accounted for by the influence of the nondiffusible ions. Hemoglobin and the organic phosphates together make up about half of the base-combining power of the cells. The hemoglobin and organic phos-

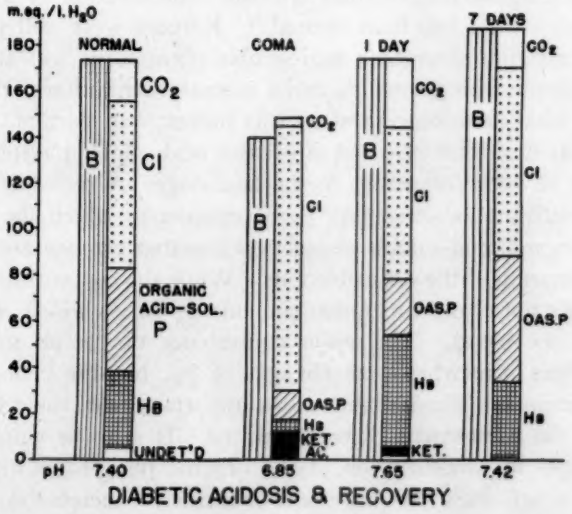


Chart 4.—Acid-base composition of the blood cells of the diabetic patient E. W., in coma and on the first and seventh days of recovery. *B* represents total base; *Hb* hemoglobin; *Ket.*, ketone acids; other symbols, as in charts 3 and 4.

phates, being less active osmotically than the diffusible ions, osmotic equality between the cells and the plasma is attained by virtue of the fact that the concentration of base per liter of water is slightly higher in the cells than in the serum.

Chart 4 presents data on the acid-base composition of the cells of three samples of blood of the patient whose urinary analysis was presented earlier. Normal cells are represented in the first column. The p_H of the serum of the first sample was 6.85. In the cells of the first sample the concentration of total base was very low, and there was a striking abnormal distribution of anions: The concentration of chloride was high, 114.7 milliequivalents per liter of water; the ketone acids

amounted to approximately 12 milliequivalents, and the carbon dioxide content was significantly reduced. There was a great reduction in concentration of the organic acid-soluble phosphorus, and the anion equivalency of the hemoglobin was low at this p_H. One day later, after the state of acidosis had been corrected by the administration of sodium bicarbonate as well as by the effects of insulin, the p_H of the blood was high, 7.65; the carbon dioxide content was high, and the concentration of total base in the cells was approximately normal. Overadjustment of the p_H and of the carbon dioxide content of the blood as shown here is found commonly at one time or another during recovery from diabetic acidosis, even without the administration of sodium bicarbonate. At this p_H the anion equivalency of the hemoglobin is high, and with a shift of diffusible ions occurring according to the Donnan law the concentration of chloride was reduced to a little less than normal.[4b] Ketones were still present, and the concentration of organic acid-soluble phosphorus was still low. In the last sample with normal p_H and a normal distribution of the diffusible ions, the total ionic concentration was higher than normal, with a high concentration of total base and of organic acid-soluble phosphorus. This also may be seen frequently in the late stages of recovery.

Especially noteworthy here is the manner in which the hemoglobin and the organic acid-soluble phosphorus together compensate for changes in concentration of the diffusible ions. While the concentration of hemoglobin does not change, its anion equivalency varies widely with changes in p_H of the blood. The anion equivalency of the phosphoric esters also changes somewhat with changes of p_H, but the changes in their concentration are considerably more important than their buffer properties in the adjustments here illustrated. It is to be emphasized that the changes in concentration of the organic phosphates are dependent on enzyme activities which are part of the active metabolism of the cells. This is a dynamic mechanism, in contrast with the apparently passive process of simple diffusion by which the concentrations of the diffusible electrolytes in the cells and extracellular fluids appear to be changed.

The next two charts illustrate data on changes in the distribution of phosphorus and potassium in the blood during different stages of recovery from severe diabetic acidosis.

Chart 5 illustrates changes found in the concentrations of inorganic phosphorus in the whole blood and of potassium in the blood serum of 4 patients with diabetes during the first few hours of the recovery of each from severe acidosis. In each instance the concentrations of inorganic phosphorus and of potassium were high in the first samples and decreased sharply to below normal concomitantly with increases in the carbon dioxide content of the p_H of the blood that indicated the beginning of recovery. The concentration of inorganic phosphorus in the blood of such subjects often remains low several days, throughout the

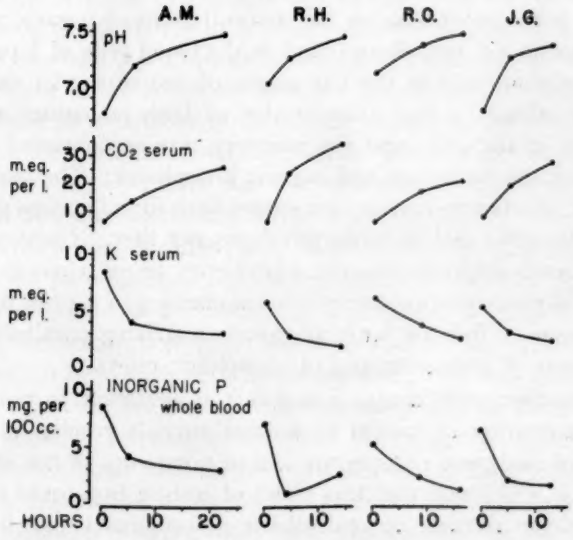


Chart 5.—Data on the blood of 4 diabetic patients (A. M., R. H., R. O. and J. G.) in severe acidosis and during early stages of recovery.

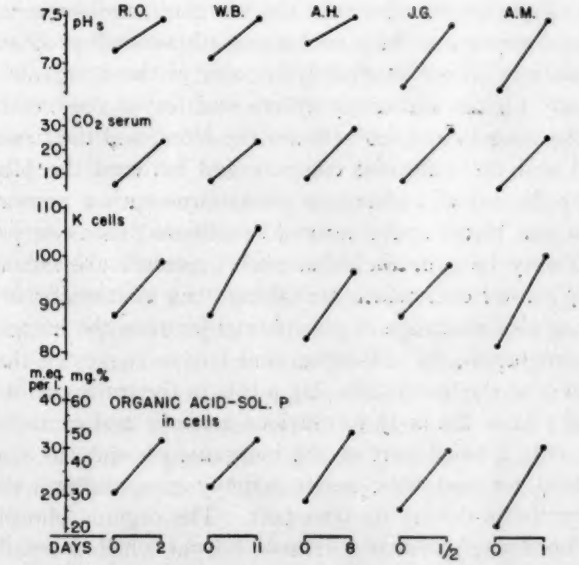


Chart 6.—Data on the blood of 5 diabetic patients (R. O., W. B., A. H., J. G. and A. M.) in severe acidosis and after recovery.

period in which the urinary excretion of phosphorus is abnormally low and in which the organic phosphates are slowly restored in the cells.

Chart 6 illustrates data on the concentrations of organic acid-soluble phosphorus and of potassium found in the blood cells of 5 patients with diabetes in coma and in the late stages of recovery. In each instance there was initially a low concentration of both potassium and organic phosphates in the cells, and the recovery was accompanied by parallel increases of the potassium and organic phosphates. The concentrations of organic phosphates here are expressed both in milligrams per hundred cubic centimeters and in milliequivalents per liter. Conversion to the latter values is approximate, the equivalency being taken as two thirds of the molal concentration irrespective of changes in p_H, but this approximation serves to indicate fairly accurately a striking parallelism between the increases of potassium and of phosphoric esters.

In connection with charts 5 and 6 it is pertinent to point out that the administration of insulin to normal animals results in a transient decrease of inorganic phosphorus and of potassium in the blood serum. Recently it was found that this effect of insulin in normal rats is associated with an increase of acid-soluble phosphorus in the liver.[6]

COMMENT

It is well to consider here the role of these phosphorus compounds of the blood in the phosphorus metabolism of the whole body. An exchange of phosphorus between the inorganic and organic phosphates of the blood appears to be a continuous physiologic process. Through the enzymatic reactions of glycolysis some of the inorganic phosphorus of the blood plasma constantly enters and leaves the blood cells while some of it passes to and fro between the blood and the tissues, between the blood and the intestinal contents and between the blood and the urine. By the use of radioactive phosphorus such a turnover of phosphorus in the blood under normal conditions has been proved to be rapid. It may be presumed that such processes are representative of essentially similar ones which are taking place continually in the tissues. Considering this exchange of phosphorus between the inorganic and the organic compounds, my colleagues and I have suggested that the phosphoric esters in the blood cells play a role in the transport of phosphorus hither and yon in the body for various anabolic and catabolic processes. Probably only a small part of the inorganic phosphorus that is carried in the blood for metabolic needs actually goes through the stages of organic synthesis during its transport. The organic phosphates in the cells do, however, serve as a reservoir from which a small amount of

6. Nelson, N.; Rapoport, S.; Guest, G. M., and Mirsky, I. A.: The Influence of Fasting, Epinephrine and Insulin on the Distribution of Acid-Soluble Phosphorus in the Liver of Rats, J. Biol. Chem. **144**:291-296 (July) 1942.

inorganic phosphorus is constantly taken out and replaced. In this respect the organic phosphates can be compared to the bicarbonate of the blood, which serves as a reservoir for the carbon dioxide, a small amount of which is withdrawn and replaced each time the blood circulates through the lungs and body tissues. In accord with this analogy, we have noted in a number of conditions a striking reciprocal relationship between the concentrations of chloride and organic acid-soluble phosphorus in the blood cells that is comparable to that found between the chloride and the bicarbonate in the blood plasma.[4a]

In conclusion, I should like to indulge in speculation on the implications of these studies beyond the premises outlined by the material presented. The data discussed may be regarded as leads which carry one beyond the problems of phosphorus metabolism and of electrolyte chemistry, which here have been linked together. As new technics for quantitative studies of enzyme activities become available, there are increasing possibilities for learning more about the functional disturbances which occur during acute and chronic illnesses due to infections, vitamin deficiencies, deficiencies of internal secretions and other causes. Examples of such technics which already have yielded valuable information can be cited, but they are still too few.

Enzymatic processes of phosphorylation are known to be essential in tissue respiration, in muscle glycolysis, in the formation and breakdown of glycogen in the liver and in the metabolism of lipids. These enzyme activities may be subject to various conditions in the medium, such as p_H and concentrations of chloride, magnesium and other constituents, and these in turn are influenced by various endogenous and exogenous factors in the metabolism of the body. Some enzymatic processes are known to be affected by internal secretions. Of the vitamins at least three are known to be utilized or to exert their effect in the body as phosphorylated compounds, namely, thiamine, riboflavin and nicotinic acid (niacin). Investigations of such enzymatic processes and conditions affecting them for the most part remain in the hands of physiologists who are primarily interested in normal physiology.

Recently reported studies of blood amylase activity have marked an advance in linking variations in activity of this enzyme with the pathologic states of certain diseases of infants. Variations in blood phosphatase in rickets and parathyroid disease are well known. Several years ago I reported great variations in the rate of glycolysis in the blood of infants suffering from various diseases [7] but the significance of those

7. Guest, G. M.: Studies of Blood Glycolysis: I. Sugar and Phosphorus Relationships During Glycolysis in Normal Blood, J. Clin. Investigation **11**:555-569 (May) 1932; II. Sugar and Phosphorus Relationships During Glycolysis in the Blood of Infants and Children with Various Diseases, ibid. **11**:571-587 (May) 1932.

observations is still obscure. One could cite other examples of conditions in which progressive changes in composition of cells and fluids of the body reflect abnormal enzyme activity, although little is known about the enzymatic reactions presumed to be responsible.

Inasmuch as the composition of living tissues is always changing, never static, alterations in rate and direction of changes in a given constituent may have greater significance than the absolute value for the concentration of that substance at a given time. Such a thesis introduces a factor of relativity into the measurements of the chemical composition of the body tissues in health and in disease. More investigations in the chemistry of the enzymes along the lines here indicated should help physicians to recognize better the significance of such qualities of changing characteristics of the body tissues and fluids in disease and so to understand more fully the significance of functional derangements and their consequences.

Children's Hospital.

LONG TERM GROWTH OF DIABETIC CHILDREN

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Most of the published studies on the growth of diabetic children appeared in the early years following the discovery of insulin.[1] The authors all stressed the fact that diabetic children tend to be overheight at the onset of the disease. However, Boyd and Kantrow [2] and Boyd [3] more recently stated that there is no characteristic overgrowth of diabetic children when symptoms are first observed. It must be borne in mind that comparisons with "expected growth" are based entirely on comparisons of average growth of children of comparable age and for comparable periods of observation. Slight variations, therefore, cannot be considered significant.

Joslin, Root and White [1a] compared the growth of their patients in preinsulin and postinsulin days, and showed what a dramatic improvement had taken place. They felt that longer periods must elapse before conclusions could be drawn as to the extent of the increase in height that they had demonstrated since using insulin. Joslin, Root and White,[1a] Boyd and Nelson [1b] and Priesel and Wagner [1f] found that growth was

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From the Children's Diabetic Clinic and the Department of Pediatrics, Mount Sinai Hospital, and the Metropolitan Life Insurance Company.

1. (*a*) Joslin, E. P.; Root, H. F., and White, P.: Growth, Development and Prognosis of the Diabetic Child, J. A. M. A. **85**:420 (Aug. 8) 1925. (*b*) Boyd, J. D., and Nelson, M. V.: Growth Studies of Children with Diabetes Mellitus, Am. J. Dis. Child. **35**:753 (May) 1928. (*c*) Spencer, H.: Diabetes Mellitus in Children: Studies of Height and Weight Charts of Forty-Five Patients, ibid. **36**:502 (Sept.) 1928. (*d*) Ladd, W. S.: Growth in Children with Diabetes Mellitus, ibid. **32**:812 (Dec.) 1926. (*e*) Rabinowitch, I. M., and Bazin, M. V.: Studies of the Rate of Skeletal Growth in Juvenile Diabetics, Arch. Dis. Childhood **4**:125 (June) 1929. (*f*) Priesel, R., and Wagner, R.: Körperbau, Wachstum und Entwicklung diabetischer Kinder, Ztschr. f. Kinderh. **41**:267, 1926. (*g*) Fischer, A. E.: The Treatment of Juvenile Diabetes, Am. J. Dis. Child. **38**:323 (Aug.) 1929.

2. Boyd, J. D., and Kantrow, A.: Progress Studies in Diabetes Mellitus in Childhood, Am. J. Dis. Child. **50**:799 (Sept.) 1935; Retardation of Growth in Diabetic Children, ibid. **55**:460 (March) 1938.

3. Boyd, J. D.: Diseases of the Pancreas—Diabetes, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 3, chap. 12.

satisfactory, but others (John,[4] Rabinowitch and Bazin [1e] and Fischer [1g]) found that diabetic children did not grow at the normal rate. McGavin and co-workers [5] stated that among the patients observed by them more boys than girls fell below normal standards of height after four years of treatment. A recent study by Brown and Thompson [6] of 60 diabetic children and adolescents whose diabetes began before 15 years of age showed that on the average they displayed no consistent deviations from normal average growth. These patients, at the time of the study, had a mean duration of the disease of four years and nine months. They were Minnesota children and with respect to the characteristics observed were representative of the child population of that state.

CASE MATERIAL

The Children's Diabetic Clinic at Mount Sinai Hospital was started in 1927, and accurate data on the growth and development of diabetic children have been kept since that time. This study is based on the records of 44 patients, 23 boys and 21 girls, all of whom (with 1 exception) were less than 13 years old at first observation. The youngest child in the series was 11 months old. We have included in this paper the data only of those patients whom we have treated regularly for at least five years; some have been treated for more than ten and 1 for fourteen years. Our data therefore cover a larger proportion of the life span of the diabetic child than other reported studies have covered. Also, in contrast to some of the other published studies, these children all came from low income families, about one third of them aided by charitable or government agencies. Twenty-eight children (63 per cent) were Jewish. A significant proportion of the non-Jewish children were from stocks that are relatively short, namely, Italian and Puerto Rican.

All but 2 of the children were admitted to the hospital ward as soon as their diabetes was discovered; they remained from four to six weeks, or until the disease was well controlled. Afterward they were seen at approximately monthly intervals in the outpatient clinic, where they were weighed and measured and had their diet checked and the dosage of insulin regulated.

In 1927, when this study began, we were prescribing a diet in which 20 to 25 per cent of the calories were in the form of carbohydrate, 10 to 15 per cent in protein and the remainder in fat. We gradually permitted our patients to take more carbohydrate, so that during the last few years their diets contained 40 per cent of the calories in carbohydrate, 15 per cent in protein and 45 per cent in fat (antiketogenic-ketogenic ratio almost 2:1). Each child's caloric requirements were determined by the Pirquet system of nutrition, in which the sitting height of the child in centimeters is used as the basis for the calculation of the diet. The diet supplied on an average 25 to 30 calories per pound daily for younger

4. John, H. J.: Growth of Diabetic Children, Am. J. Digest. Dis. & Nutrition **1**:855 (Feb.) 1935.

5. McGavin, A. P.; Schultz, E.; Peden, G. W., and Bowen, B. D.: The Physical Growth, the Degree of Intelligence and the Personality Adjustment of a Group of Diabetic Children, New England J. Med. **223**:119 (July 25) 1940.

6. Brown, G. D., and Thompson, W. H.: The Diabetic Child—An Analytical Study of His Development, Am. J. Dis. Child. **59**:238 (Feb.) 1940.

children and 20 to 25 calories per pound for older ones. The protein content (15 per cent) varied from 2 Gm. per pound (4+ Gm. per kilogram) for infants to a little more than 1 Gm. per pound (2+ Gm. per kilogram) for children in the preadolescent years. Each mother was instructed in methods of weighing and substituting food while the child was under treatment in the hospital ward. Although the diet was prescribed and was supposed to have been weighed accurately at home, we were under no illusion that additional amounts of food were not taken. Nevertheless, we felt that a prescribed diet was of value as a working basis, even for those children who were uncooperative. Regular attendance at the clinic and home visits by the social service worker helped in maintaining morale and diabetic control.

All children received insulin from the onset of treatment. A few patients in the first years of our experience were treated with diet alone for a few months after their initial hospitalization. At first we used one, two or three (rarely four) doses of regular insulin. Later we employed protamine zinc insulin or combinations of protamine zinc and regular insulin or, more recently, crystalline insulin. The urine was kept nearly free of sugar during the first months of illness. After the first year this became increasingly difficult, especially during the winter months when the children were less active. In general, the children required more insulin as their body height and weight increased. After puberty was established and growth fully developed, the dose remained fairly constant. The patients who had the usual childhood diseases were treated at home, except a few who had to be hospitalized for treatment of ketosis.

HEIGHT AND WEIGHT STANDARDS USED

The Woodbury standard (for age 5 years or under) and the Baldwin-Wood tables (for age 5 years and over) were used as standards of weight.[7] Children have been classified in build groups representing certain degrees of departure from average weight for height as follows: Slight underweight or overweight was represented by a deviation under 5 years of age of 4 to 6 pounds, from 5 to 9 years of 5 to 8 pounds, and from 10 to 19 years of 5 to 14 per cent. Moderate underweight or overweight has been considered present when the child was 7 pounds or more underweight or overweight at 5 years, 9 pounds or more from 5 to 9 years and 15 per cent or more from 10 to 19 years.[9] The weaknesses of the use of average weights for children are fully realized, but for comparisons of this type, the purpose of which is to show the distribution of weights around a mean, the use of such averages is valid.

Burgess charts[10] were used for height standards. Children have been classified as tall if they exceeded the median line by more than 1 inch, and short if they were more than 1 inch below the standard. The Burgess standards are composite, computed from several tables. The median heights by these standards are somewhat higher than those of earlier tables but lower than those of other recently published tables relating to children in the Middle West and to better class chil-

7. Baldwin, B. T.; Wood, T. D., and Woodbury, R. M.: Weight-Height-Age Tables, Mother & Child, July 1923, supp.

8. Footnote deleted by authors.

9. Joslin, E. P.; Dublin, L. I., and Marks, H. H.: Studies in Diabetes Mellitus: IV. Etiology, Am. J. M. Sc. **191**:759 (June) 1936; **192**:9 (July) 1936.

10. Burgess, M. A.: Construction of Two Height Charts, J. Am. Statist. A. **32**:290, 1937.

dren. In view of the poor socioeconomic status of the families from which the children in this study came, the Burgess standards appear to be proper for the evaluation of their height and growth. It may be noted, moreover, that the annual or cumulative increments of growth during the age range covered by this study are not greatly different in the various standard tables. The reason for this is that in the more recent tables the height is established at a level above early standards at comparatively young ages, and this advantage is simply maintained at the higher ages. The nearest birth anniversary at the time of the earliest symptoms of diabetes determines the "age at onset."

HEIGHT AT ONSET

Because of the type of onset of diabetes in childhood, the heights at first observation may be considered as "height at onset." The period between the onset of diabetic symptoms and the first visit to the clinic is usually so short that the difference between arrested and normal growth is insignificant. For these reasons the height measurement taken at the first examination closely approximates the actual "height at onset." Only 5 of the girls and 3 of the boys were classified as "short at onset." Two of these girls, A. S.[11] (D [2]), and E. S. (G [2]), were seen three and four years respectively after the onset of their disease. They had been poorly regulated, and although their heights at onset of the diabetes were not known, it is apparent that they had grown very little before we had seen them. Of the other 42 patients, all but 3 of the boys and 3 of the girls were either average or tall for their age when diabetes began. Of the 23 boys, 12 were tall, 4 of them 3 inches or more above the average. Of the 21 girls, 9 were tall, 6 of them 3 inches or more above their average. The only really striking deviation from average was E. S. (J [2]), who at the age of 12 years was 7¼ inches (18.4 cm.) taller than average; his parents, Scandinavians, were both over 6 feet (180 cm.) tall. They stated that he did not grow unusually during the year preceding the onset of his diabetes. Facts on growth in the period preceding the onset are generally difficult to obtain. It is our impression, but only an impression, from carefully taken histories that the children observed did not grow rapidly just before their diabetes began.

Our patients, nearly all of whom were the children of immigrant parents, showed the same height relationship to their parents as do nondiabetic children. Boas[12] demonstrated that offspring of immigrant Jews from Eastern Europe are usually taller than their parents. The generally accepted explanation for this is the better hygiene and larger caloric intake during the infancy and childhood of the new generation.

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11. A. S. has grown very little. She has a very large liver and spleen. Details of her case will be described in a separate communication.

12. Boas, F.: Changes in Bodily Form in Descendants of Immigrants, United States Senate Documents, Washington, D. C., Government Printing Office, 1910, p. 22.

GROWTH IN HEIGHT

Growth of these children is shown on charts (Burgess) 1 and 2. Only the height at onset and at the last examination appear here, and the points are joined by a straight (dotted) line. The growth curve for all patients was fairly regular. Slight retardations or accelerations were insignificant over the years. Moreover, these measurements, even though made carefully and at the same hour of the day, may vary slightly depending on the posture of the child when examined. Estimates made for short periods, therefore, may seem to indicate spurts or lags of growth which actually are spurious. For these reasons intermediate growth figures were not charted.

As can be seen from the median line, the normal curve for girls reaches its peak during the fourteenth year, and growth gradually ceases at about the seventeenth birthday. For boys the period of maximum growth is during the fifteenth and sixteenth years, and growth ceases about the twentieth year. Slight growth may occur beyond these years, but it is probably too small to affect these comparisons appreciably. The figures for yearly growth (not shown here) indicate that diabetic children have about the same spurt of growth during puberty as nondiabetic children. Closure of the epiphyses in diabetic children takes place at the usual time. One would expect, therefore, that growth would gradually cease as it does in nondiabetic children. This was found to be the case.

From charts 1 and 2 and the corresponding tables, it will be seen that the average rate of growth of both boys and girls in this series, who have been followed for a comparatively long period of time, was generally below that expected. Thus the gain in height of 10 of the boys was over 1 inch less than the average based on the composite standard of Burgess. Only 4 boys exceeded the average growth by such an amount. These were E. S. (J [2]) and A. I. (I [2]), both of whom were tall at onset, and J. L. (A [1]) and L. S. (G [2]), both of whom were short at onset. The growth of the remaining 9 boys was average, that is, within an inch of the average of the Burgess standards. Several boys grew very slowly. H. C.'s growth was 8 inches (20 cm.) less than average after ten years of conscientious care and treatment. He did not have any unusual illnesses and was never in diabetic ketosis; he was not a hepatomegalic dwarf. G. S. (G [1]) and M. T. (H [1]) as well as M. P. (B [1]) grew 3 to 4 inches (7.5 to 10 cm.) less than average. They were apparently as well cared for as the others in the group.

Likewise, of the 21 girls the increase in height of 10 during the period of observation was more than 1 inch (2.5 cm.) below the average set by the Burgess standards. For 7 girls the height increase was

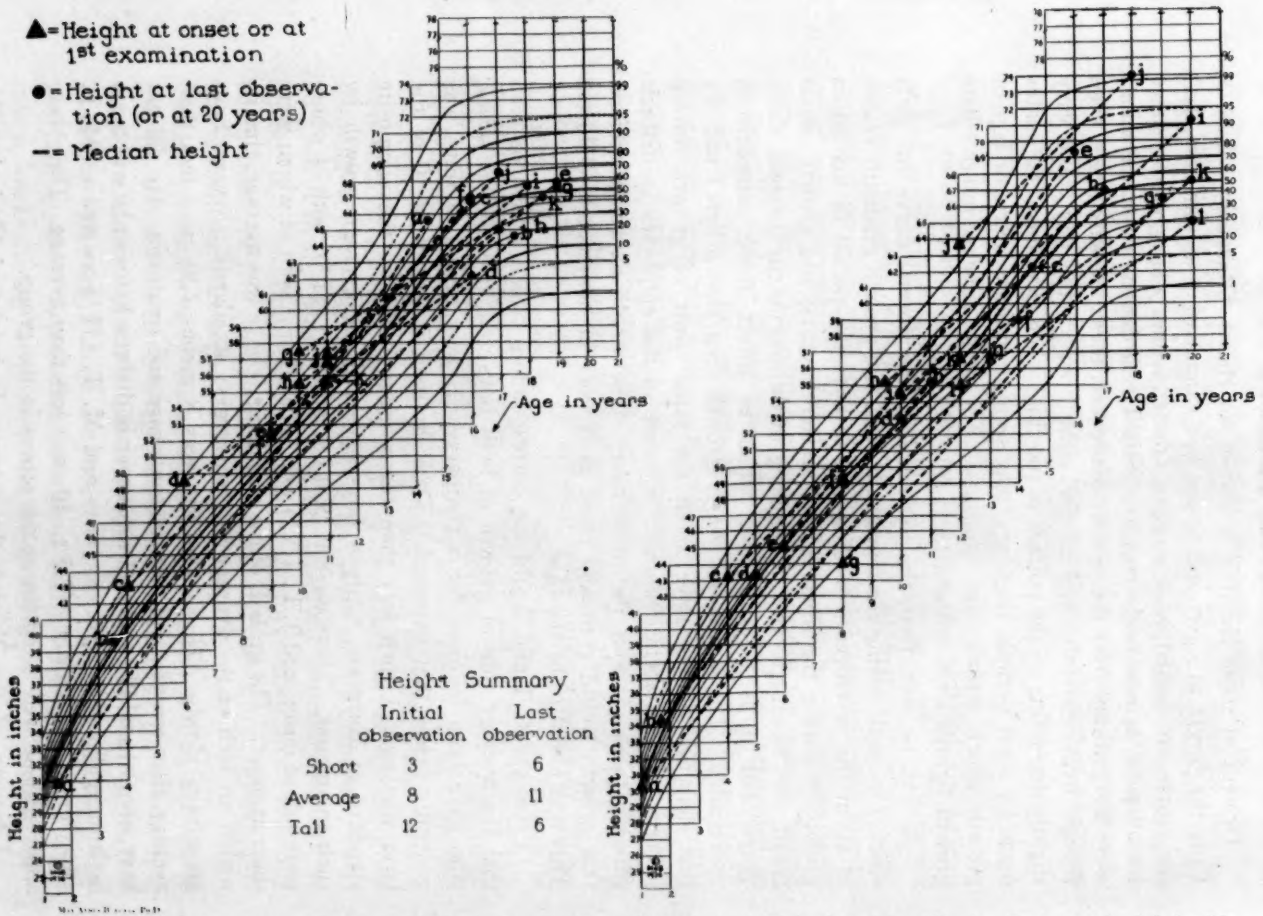

Chart 1.—Height summary for 23 diabetic boys. (Detailed data are to be found in table 1. Cases on the left in this chart are designated by superscript 1 in the table; those on the right, by superscript 2.)

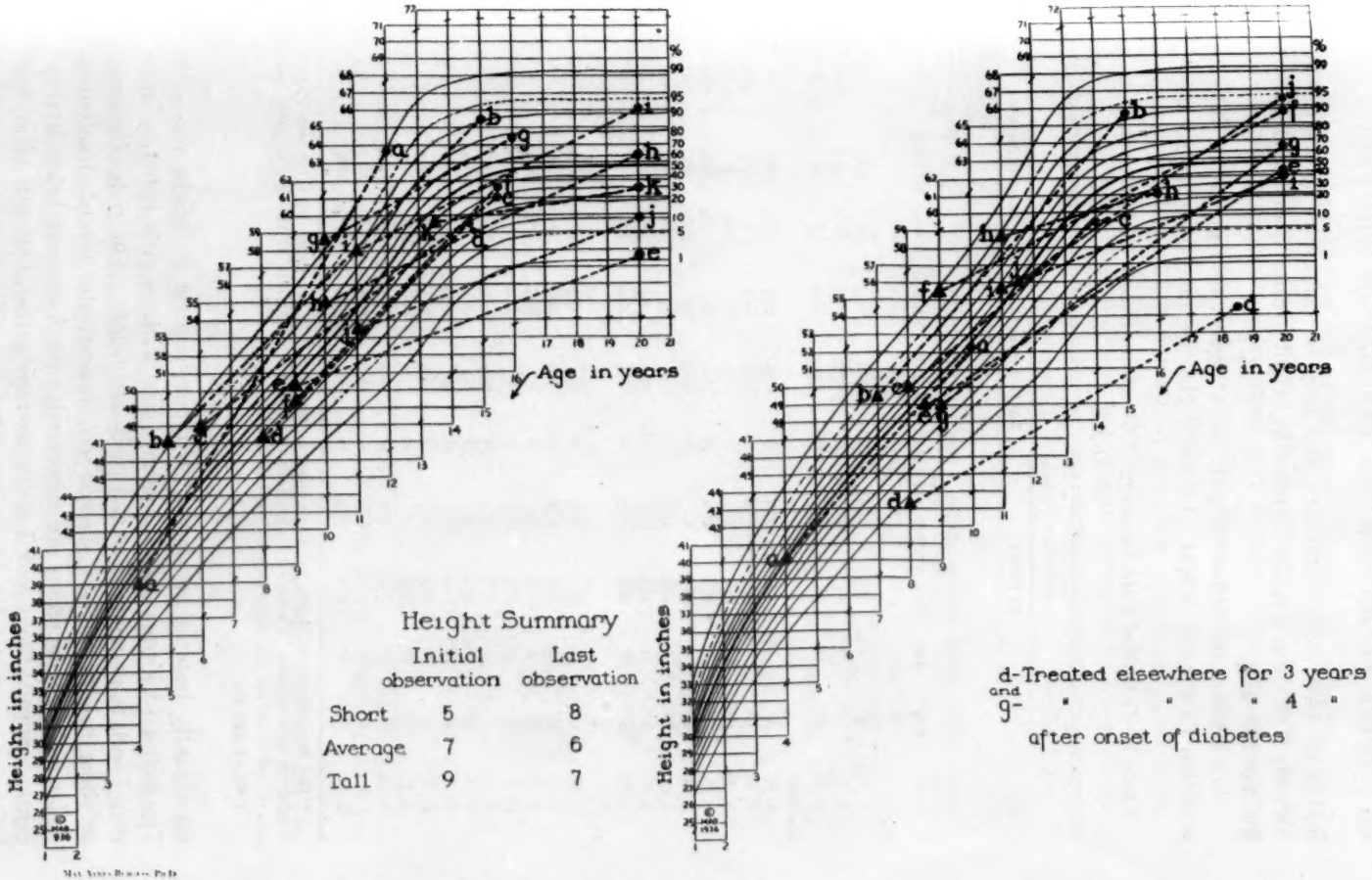

Chart 2.—Height summary for 21 diabetic girls. (Detailed data are to be found in table 2. Cases on the left in this chart are designated by superscript 1 in the table; those on the right, by superscript 2.)

within an inch of this standard and may be considered average, but for only 4 of them was the increase in height greater than 1 inch above the average gain.

The record was worse for girls tall at onset; they generally did not maintain their extra height. Of the 9 girls in this group, only 1 grew

TABLE 1.—*Individual Case Summary of Growth in Height (All Measurements in Inches)*

		Boys								
		At Onset			At Last Observation †			Gain in Height		
Height Group; Case	Key *	Age	Height Actual	Height Normal	Age	Height Actual	Height Normal	Actual	Normal	Deficiency Below or Excess Over Normal Gain
Short										
J. L.	A^1	1½	30¾	32½	14½	65¾	62¼	35	29¾	+5¼
L. S.	G^1	8	44	49	19	66½	67½	22½	18½	+4
B. H.	E^1	12	55	56½	20	65	67½	10	11	−1
Average										
R. G.	A^2	1	30¼	30¼	13	56¾	58¾	26½	28½	−2
A. L.	B^2	1½	34¼	33½	11	55¼	54¾	21	21¼	−¼
M. P.	B^1	3½	39¾	39	17½	64½	67	24¾	28	−3¼
S. B.	D^2	5	43¼	42¾	10	53	53	9¾	10¼	−½
J. M.	E^2	6	45	45	18	69¼	67¼	24¼	22¼	+2
I. G.	F^2	8	49¼	49¼	14	59	61	8¾	10¾	−2
A. N.	K^1	11	55½	54¾	18½	67	67¼	11½	12½	−1
G. H.	K^2	12	56¾	56½	20	67½	67½	10¾	11	−¼
Tall										
C. L.	C^1	4	43	40½	16	67	65½	24	25½	−1½
S. E.	C^2	4	43¼	40½	14½	62¼	62¼	19	21¾	−2¾
H. C.	D^1	6	49½	45	16	62¼	65¾	12¾	20¾	−8
H. I.	E^1	9	52½	51	19	68	67¼	15½	16¼	−¾
E. L.	F^1	9	52½	51	16	67	65½	14½	14½	0
E. H.	B^2	9½	55¼	52	17	67	66¾	11¾	14¾	−3
M. T.	H^1	10	55½	53	17	65	66¾	9½	13¾	−4¼
G. S.	G^1	10	57½	53	19	67¾	67¼	10¼	14¼	−4
A. I.	I^2	10	54½	53	20	71¼	67¾	16¾	14¾	+2
N. G.	I^1	11	57¼	54¾	18	67¾	67¼	10½	12½	−2¼
I. N.	J^1	11	56¾	54¾	17	68½	66¾	11¾	12	−¼
E. S.	J^2	12	63¾	56½	18	74	67¼	11¼	10¾	+½

* The key refers to chart 1. Each case is identified by the letter and the superscript number in this column. Cases with superscript 1 are on the left side of the chart; those with superscript 2 are on the right side of the chart.

† Or at age 20.

significantly faster than normal, but her increase in height was only 1½ inches (3.8 cm.) above average. Six of these girls failed by more than 1 inch to maintain normal growth and height. The girls of average or short height at onset showed a comparatively normal distribution so far as height increases are concerned, with 4 showing below average gains, 5 normal gains and 3 above average gains. One girl of average height at onset, E. M. (A^1), exceeded her average expected growth by 7¾ inches (19.7 cm.) in a period of eight years.

As a result of the failure of these children to maintain, on the average, a normal increase in height, they tended to show at last observation a normal distribution with respect to height, in contrast to the tendency to be tall at onset (first column of tables 1 and 2).

TABLE 2.—*Individual Case Summary of Growth in Height (All Measurements in Inches)*

Height Group; Case	Key *	Girls: At Onset: Age	At Onset: Height: Actual	At Onset: Height: Normal	At Last Observation †: Age	At Last Observation †: Height: Actual	At Last Observation †: Height: Normal	Gain in Height: Actual	Gain in Height: Normal	Gain in Height: Deficiency Below or Excess Over Normal Gain
Short										
D. K.	D^1	8	47¼	48¼	14½	59½	61¾	12¼	13	—¾
A. S.‡	D^2	8	43¼	48¾	18½	54½	62¾	9¼	14	—4¾
M. B.	F^1	9	49¼	50¾	15½	61½	62½	12¼	11¾	+½
E. S.‡	G^2	9	49	50¾	20	63¾	63	14¾	12¼	+2½
S. H.	J^1	11	53½	54¾	20	60¼	63	6¾	8¼	—1½
Average										
E. M.	A^1	4	39	40	12	63¾	57	24¾	17	+7¾
M. S.	A^2	4	40¼	40¼	10	52¼	52¼	8	8	—
S. S.	E^2	8½	49	49¾	20	62½	63	13½	14¼	—¾
G. K.	E^1	9	50¼	57½	20	50½	63	7¼	12½	—5¼
M. S.	I^2	11	55¾	54¾	20	62	63	6¼	8¼	—2
B. B.	J^2	11½	56	56	20	63½	63	10½	7	+3½
E. M.	K^1	13½	59½	60½	20	61¾	63	2¼	2½	—¼
Tall										
D. T.	B^1	5	47	42¼	15	65¼	62	18¼	19¾	+1½
M. S.	C^1	6	48	44¾	15½	61	62½	13	17¾	—4¾
S. L.	B^2	7	49½	46¾	15	65¾	62	16¼	15¼	+1
S. R.	C^2	8	50	48¾	14	59½	61	9½	12¼	—2¾
M. J.	F^2	9	55½	50¾	20	65¾	63	10¼	12¼	—2
J. Z.	H^1	10	55	52½	20	63½	63	8½	10½	—2
P. B.	G^1	10	58¾	53	16	64½	62¾	5¾	9¾	—4
G. G.	I^1	11	58	54¾	20	66	63	8	8¼	—¼
R. K.	H^2	11	58¾	54¾	16	61	62¾	2¼	8	—5¾

* The key refers to chart 2. Each case is identified by the letter and the superscript number in this column. Cases with superscript 1 are on the left side of the chart; those with superscript 2 are on the right side of the chart.

† Or at age 20.

‡ A.S. and E. S. were treated elsewhere for three and four years respectively after the onset of diabetes.

WEIGHT AT FIRST OBSERVATION

The data on weight at first observation are presented as a matter of interest. They certainly may not be taken as weights at onset, because practically all children lose weight between onset and first observation as a result of polyuria and glycosuria. The actual loss of weight varies considerably with the severity and the duration of the diabetic symptoms. Unless one has a record of the child's exact weight before symptoms began, the actual weight lost can be judged only from the parents' statements. It is not surprising, therefore, that most of the weights at first

TABLE 3.—*Data for Computations of Deviations from Average Weight of Boys*

Height Group; Case	At First Observation						At Last Observation					
	Age	Height, Inches	Weight, Pounds: Actual	Weight, Pounds: Normal	Pounds Under (—) or Over (+) Normal	Weight Class *	Age	Height, Inches	Weight, Pounds: Actual	Weight, Pounds: Normal	Pounds Under (—) or Over (+) Normal	Weight Class *
Short												
J. L.	1½	30¾	22	23	— 1	Av.	14½	65¾	124	125	— 1	Av.
L. S.	8	44	39	44	— 5	Sl.Un.	19	63½	133	141	— 8	Sl.Un.
B. H.	12	55	61	74	—13	Mo.Un.	20	65	112	137	—25	Mo.Un.
Average												
R. G.	1	30¼	20	22	— 2	Av.	12	56¾	84	82	+ 2	Av.
A. L.	1½	34¼	26	27	— 1	Av.	11	55¼	76	73	+ 3	Av.
M. P.	3½	39¾	42	36	+ 6	Sl.Ov.	17½	64½	118	129	—11	Sl.Un.
S. B.	5	43¼	38	41	— 3	Av.	10	53	71	67	+ 4	Sl.Ov.
J. M.	6	45	33	46	—13	Mo.Un.	18	69¼	135	149	—14	Sl.Un.
I. G.	8	49¼	46	55	— 9	Mo.Un.	14	59	85	90	— 5	Sl.Un.
A. N.	11	55½	63	75	— 9	Sl.Un.	18½	67	135	142	— 7	Av.
G. H.	12	56¾	66	71	—15	Mo.Un.	20	67½	118	148	—30	Mo.Un.
Tall												
C. L.	4	43	37	41	— 4	Sl.Un.	16	67	110	134	—24	Mo.Un.
S. E.	4	43¼	38	41	— 3	Av.	14½	62¼	99	104	— 5	Av.
H. C.	6	49½	55	56	— 1	Av.	16	62¼	119	107	+12	Sl.Ov.
H. I.	9	52½	57	65	— 9	Mo.Un.	19	68	125	147	—22	Mo.Un.
E. L.	9	52½	69	66	+ 3	Av.	16	67	126	134	— 8	Sl.Un.
E. H.	9½	55¼	74	73	+ 1	Av.	17	67	130	136	— 6	Av.
M. T.	10	55½	78	75	+ 3	Av.	17	65	144	127	+17	Sl.Ov.
G. S.	10	57½	110	82	+28	Mo.Ov.	19	67¾	168	147	+21	Sl.Ov.
A. I.	10	54½	52	72	—20	Mo.Un.	20	71¼	135	162	—27	Mo.Un.
N. G.	11	57¼	69	81	—12	Sl.Un.	18	67¾	126	143	—17	Sl.Un.
I. N.	11	56¾	70	81	—11	Sl.Un.	17	68½	132	143	+11	Sl.Ov.
E. S.	12	63¾	112	109	+ 3	Av.	18	74	151	170	—19	Sl.Un.

* The basis of weight classification for overweight and underweight is deviation from average weight.

	Under 5	5 to 9	10 to 20
Slight.....	4 to 6 pounds	5 to 8 pounds	5 to 14%
Moderate.....	7 pounds or more	9 pounds or more	15% or more

Weight standards: Under age 5, Woodbury; ages 5 and over, Baldwin and Wood.

TABLE 4.—*Data for Computations of Deviations from Average Weight of Girls*

Height Group; Case	At First Observation						At Last Observation					
	Age	Height, Inches	Weight, Pounds: Actual	Weight, Pounds: Normal	Pounds Under (—) or Over (+) Normal	Weight Class *	Age	Height, Inches	Weight, Pounds: Actual	Weight, Pounds: Normal	Pounds Under (—) or Over (+) Normal	Weight Class *
Short												
D. K.	8	47¼	38	50	—12	Mo.Un.	14½	59½	90	103	—13	Sl.Un.
A. S.†	8	43¼	46	41	+ 5	Sl.Ov.	18½	54½	105	100	+ 5	Sl.Ov.
M. B.	9	49¼	50	55	— 5	Sl.Un.	15½	61½	117	114	+ 3	Av.
E. S.†	9	49	47	55	— 8	Sl.Un.	20	63¾	120	127	— 7	Sl.Un.
S. H.	11	53½	63	70	— 7	Sl.Un.	20	60¼	116	115	+ 1	Av.
Average												
E. M.	4	39	29	34	— 5	Sl.Un.	12	63¾	98	114	—16	Sl.Un.
M. S.	4	40¼	31	36	— 5	Sl.Un.	10	52½	65	64	+ 1	Av.
S. S.	8½	49	54	55	— 1	Av.	20	62½	126	123	+ 3	Av.
G. K.	9	50¼	53	58	— 5	Sl.Un.	20	57½	118	108	+10	Sl.Ov.
M. S.	11	55¾	68	78	—10	Sl.Un.	20	62	111	122	—11	Sl.Un.
B. B.	11½	56	82	79	+ 3	Av.	20	66½	148	137	+11	Sl.Ov.
E. M.	13½	59½	69	99	—30	Mo.Un.	20	61¾	134	122	+12	Sl.Ov.
Tall												
D. T.	5	47	74	49	+25	Mo.Ov.	15	65¼	136	122	+14	Sl.Ov.
M. S.	6	48	47	52	— 5	Sl.Un.	15½	61	110	112	— 2	Av.
S. L.	7	49½	57	55	+ 2	Av.	15	65¾	123	125	— 2	Av.
S. R.	8	50	52	57	— 5	Sl.Un.	14	59½	116	99	+17	Mo.Ov.
M. J.	9	55½	63	75	—12	Mo.Un.	20	65¾	125	134	— 9	Sl.Un.
J. Z.	10	55	68	74	— 6	Sl.Un.	20	63½	113	125	—13	Sl.Un.
P. B.	10	58¾	106	87	+19	Mo.Ov.	16	64½	144	122	+22	Mo.Ov.
G. G.	11	58	70	86	—16	Mo.Un.	20	66	157	134	+23	Mo.Ov.
R. K.	11	58¾	64	90	—26	Mo.Un.	16	61	98	112	—14	Sl.Un.

† A. S. and E. S. were treated elsewhere for three and four years respectively after the onset of the diabetes.

* The explanation of the classification is given in the footnote to table 3.

observation are below average, both among boys and girls. Thus, only 2 of the boys and 3 of the girls were overweight at first observation but 11 of the boys and 15 of the girls were underweight. While the amount of weight which these children lost before the disease was diagnosed is unknown, it is our impression that the majority of these children were not overweight when their disease began. The initial loss of weight usually was rapidly regained soon after glycosuria was controlled.

CHARACTERISTICS OF WEIGHT DISTRIBUTION AT LAST OBSERVATION

Boys.—As seen from table 5, 12 of the boys were underweight, 6 were normal and 5 were overweight when last examined. Table 3 gives the facts for each patient. Of the boys who were overweight,

TABLE 5.—*Build Grouping of Diabetic Children at First and at Last Observation (or at Age 20)*

Weight Class *	Boys		Girls	
	First Observation	Last Observation	First Observation	Last Observation
Underweight				
Moderate	6	5	5	0
Slight	5	7	10	7
Average weight	10	6	3	6
Overweight				
Slight	1	5	1	5
Moderate	1	0	2	3

* The explanation of the classification is given in the footnote to table 3.

none was more than 15 per cent above average. Of the 7 underweight boys, however, 5 were more than 15 per cent below the average for their height and age.

Girls.—In contrast with the figures for boys, 7 of the girls were underweight, 6 were normal and 8 were overweight (table 5). Details of the deviation from average weight are shown in table 4. The figures are of interest when broken up into slight and moderate overweight and underweight. Of the 8 girls who were overweight at the time of the last examination, 3 were overweight 15 per cent (moderate overweight), whereas, as just stated, none of the 5 overweight boys was more than slightly overweight. None of the girls was more than 15 per cent underweight.

The tendency of the diabetic girl to gain excessive weight during puberty is a common observation. Lande and Pollack [13] have noted

13. Lande, H., and Pollack, H.: Personal communication to the authors.

it in adolescent girls treated in the adult diabetic clinic of the hospital. Insulin dosage has been fairly constant during these years, so that one cannot ascribe the excessive gain in weight to a sudden storage in the body of glycogen and water. To the best of our knowledge, these patients did not exceed their diet any more than they may have done during their younger years, when they did not gain excessively. Since the caloric intake was not increased and the basal metabolic rates were within normal limits, the gain in weight was probably due to a lower output of energy. Decreased physical activity in the female may explain the marked tendency to obesity. The fact that boys are more active than girls probably accounts for their much lower average weight during the adolescent years.

COMMENT

Conflicting reports concerning height at onset of diabetes in children and rates of growth following the development of the disease are difficult to explain. The largest single series of cases, that of Joslin, appears to establish the fact that, in the main, diabetic children are tall for their age at the onset of the disease and, further, that the rate of growth thereafter is lower than the average for nondiabetic children. We have confirmed his findings in a smaller series of cases covering a longer period of years. Others, like Boyd, have found that diabetic children under their supervision were not above average height at the onset of the disease and did not show any constant trend in height at any time before or after onset. This fact merely serves to amplify the total picture of juvenile diabetes. There are so many variables, such as hereditary, geographic, nutritional, morbid, psychosomatic and socioeconomic factors, that the picture of the child at the onset of diabetes and his growth afterward cannot present a constant, uniform pattern but must necessarily vary as these factors vary.

Twenty of 23 boys and 16 of 19 girls for whom there were measurements within a short time of the onset of their diabetes were either average or tall. The significance of these figures is enchanced by the fact that a majority of the patients were offspring of immigrant Jews from Eastern Europe, while others were of Italian or Puerto Rican parentage, usually of short stature. All were from the low income group.

The average rate of growth of both boys and girls in our series fell below normal. It is interesting to find that measurements for the group of children studied are in line with those of Joslin and his colleagues for children from heterogeneous socioeconomic and racial groups, despite the fact that most of the children described here were from an indigent group.

There was a tendency for the boys to be underweight and for the girls to be overweight during the years of puberty. Since the caloric intake was estimated to be similar, the greater physical activity in boys may explain the differences in weights in the sexes.

SUMMARY

A group of diabetic children from low income families has been studied over a period of years; their growth characteristics are tabulated, and pertinent findings are discussed.

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RELATION OF VITAMIN C TO SCARLET FEVER, RHEUMATIC INFECTIONS AND DIPHTHERIA IN CHILDREN

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Recent reviews [1] suggest that both in experimental animals and in man a low intake of vitamins may be one of the causes of the lowering of natural resistance. This has been suggested in cases in which scurvy was manifest. Since a theoretic "prescorbutic state" has been postulated as occurring in persons with low levels of ascorbic acid in the plasma and with low urinary excretions but in whom symptoms and signs of clinical scurvy are absent, these persons are also thought to have lessened resistance. It has been presupposed, moreover, that in the course of certain infections [2] there is an increased demand for vitamin C.

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* Lieutenant Commander, Medical Corps, United States Naval Reserve.

Merck and Company, Rahway, N. J., supplied the ascorbic acid used in this investigation.

Read at the Fifty-Fourth Annual Meeting of the American Pediatric Society, Skytop, Pa., May 1, 1942.

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1. (*a*) Robertson, E. C.: The Vitamins and Resistance to Infection, Medicine **13**:123 (May) 1934. (*b*) Perla, D., and Marmorston, J.: Role of Vitamin C in Resistance, Arch. Path. **23**:543 (April); (*c*) 683 (May) 1937. (*d*) Wolbach, S. B.: Vitamin Deficiency Experimentation as Research Method in Biology, Science **86**:569 (Dec. 24) 1937.

2. (*a*) Abbasy, M. A.; Harris, L. J.; Ray, S. N., and Marrack, J. R.: Diagnosis of Vitamin-C Subnutrition by Urine Analysis: Quantitative Data—Experiments on Control Subjects, Lancet **2**:1399 (Dec. 21) 1935. (*b*) Rinehart, J. F., and Mettier, S. R.: The Joints in Experimental Scurvy and Scurvy with Superimposed Infection, with a Consideration of the Possible Relation of Scurvy to Rheumatic Fever, Am. J. Path. **9**:952 (Nov.) 1933; (*c*) The Heart Valves and Muscle in Experimental Scurvy with Superimposed Infection, with Notes on Similarity of Lesions to Those of Rheumatic Fever, ibid. **10**:61 (Jan.) 1934. (*d*) Rinehart, J. F.; Connor, C. L., and Mettier, S. R.: Further Observations on Pathologic Similarities Between Experimental Scurvy Combined with Infection, and Rheumatic Fever, J. Exper. Med. **59**:97 (Jan.) 1934.

In view of these opinions, we welcomed the opportunity to study the relation of vitamin C to acute and chronic infections in 145 hospitalized children. An additional 110 normal unhospitalized children served as controls. The clinical patients were divided into six groups as follows: Seventy-six were patients with scarlet fever; 17 were afflicted with acute rheumatic fever not involving the heart; 26 had acute rheumatic heart disease; 16 were convalescing from acute carditis; 2 had chorea, and 8 suffered from acute pharyngeal diphtheria. The normal control group consisted of healthy children of the same socioeconomic status as the patients studied.

Determinations of the ascorbic acid content of the blood plasma were made either two or three times a week during the course of the investigation. Samples of blood from a finger were taken either before breakfast or approximately five hours after a breakfast devoid of citrus fruits or other sources of vitamin C. The determinations were made by the micro method of Farmer and Abt.[3]

In the six clinical groups studied, alternate patients received a large supplement of ascorbic acid in addition to that contained in the regular hospital diet. The doses varied from 300 to 600 mg. per day, according to the ages of the patients. Since all children came from families of about the same economic status, their previous consumption of vitamin C–containing foods is assumed to have been approximately equivalent.

PATIENTS WITH SCARLET FEVER

Seventy-six patients with scarlet fever were studied at the Municipal Contagious Disease Hospital of Chicago.[4] In all instances the study was begun on or shortly after admission. The criteria used in selecting the cases for study were a temperature of 102 F. or more, a typical scarlatinal rash and the sore throat characteristic of scarlet fever. The period of confinement was four weeks or longer.

Of the patients chosen, 41 formed the control groups; the remaining 35 were given supplemental doses of ascorbic acid. In general, the patients receiving ascorbic acid showed a significant rise in the level of ascorbic acid in the blood plasma within five days, while in the control group (those receiving only the ascorbic acid in the hospital diet) the rise was usually delayed until about thirteen days after admission. The patients receiving supplements maintained higher levels in the plasma than those in the control group; in general, the clinical courses of the two groups were similar. In patients suffering from complications,

3. Farmer, C. J., and Abt, A. F.: Determination of Reduced Ascorbic Acid in Small Amounts of Blood, Proc. Soc. Exper. Biol. & Med. **34**:146 (March) 1936.

4. Through the courtesy of Dr. Archibald Hoyne, Director, Municipal Contagious Hospital, Chicago.

a delay in the rise of plasma ascorbic acid occurred in both groups (chart 1). The number of complications occurring in the group receiving ascorbic acid supplements was 41, while in the control group 45 complications occurred (table 1). The total number of days of fever with a temperature over 100 F. was 206 for the treated group and 216 for the control group.

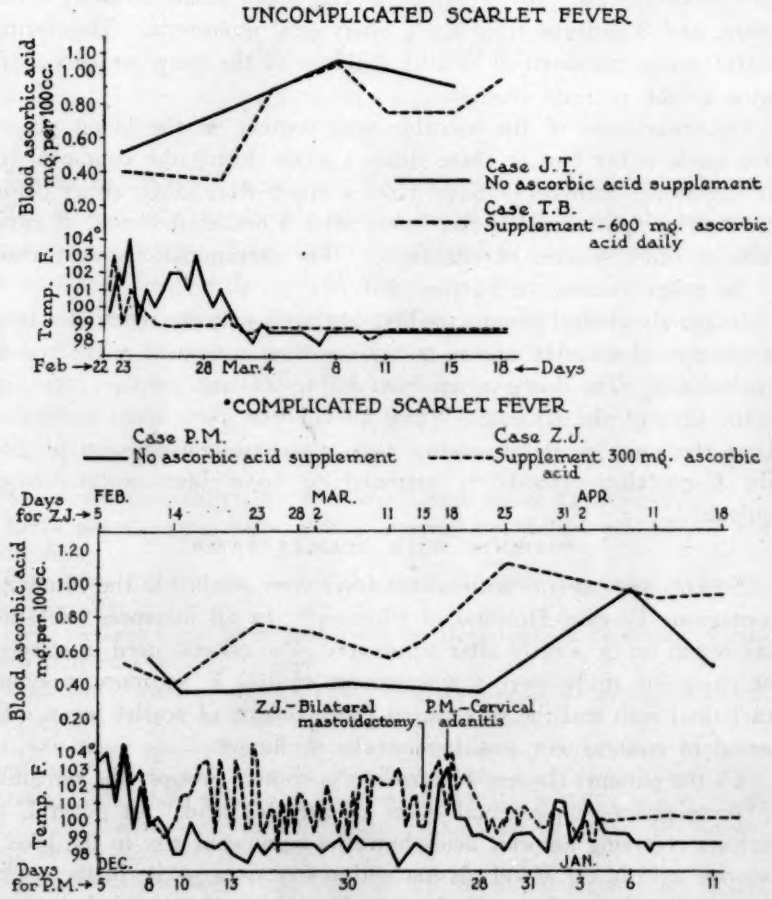

Chart 1.—Graphs of typical cases of scarlet fever, showing the depression of plasma ascorbic acid levels during infection due to complications.

The average initial value of blood plasma ascorbic acid in these patients with scarlet fever was 0.49 mg. per hundred cubic centimeters. This figure is significantly lower than that for the normal control group, which is 0.62 mg. per hundred cubic centimeters. After five to ten days' duration of the disease, the plasma ascorbic acid value for the group receiving no supplement of ascorbic acid rose to 0.57 mg. per

hundred cubic centimeters, which is not significantly lower than the value for the normal children (see table 2). The finally attained average value for this group after a four week or longer hospitalization period was 0.73 mg. per hundred cubic centimeters.

TABLE 1.—*Complications in Patients with Scarlet Fever*

Type of Complication *	Patients Receiving Ascorbic Acid Supplement		Patients Not Receiving Ascorbic Acid Supplement	
	Number	Percentage	Number	Percentage
No complications	16	45.7†	17	41.5†
Throat abscess	1	2.8	1	2.4
Otitis media	5	14.3	10	27.6
Cervical adenitis	11	31.4	15	36 6
Mastoiditis	1	2.8	3	7.3
Arthritis	2	5.7	3	7.3
Nephritis	0	...	1	2.4
Carditis	1	2.8	0	...
Deaths	0	...	1	2.4
Other complications	20	...	11	...
Number of patients in group	35		41	
Total number of complications in group	41		45	

* Certain patients suffered from more than one type of complication.

† The numbers of these patients without complication are figured as percentage of supplemented and nonsupplemented groups respectively.

TABLE 2.—*Ascorbic Acid Values in the Control Group of Children and in Those with Scarlet Fever, Rheumatic Fever and Rheumatic Heart Disease*

Type of Patient	Number of Cases	Average of Values for Plasma Ascorbic Acid, Mg. per 100 Cc.	Standard Deviation ±	Significant Difference	Change from Control
Normal control group *	110	0.62	0.039		
I. Scarlet fever patients Initial values on entering hospital	41	0.49	0.036	0.160	0.13
I. Patients with scarlet fever after 5 to 10 days' duration of disease in hospital					
Without ascorbic acid	40	0.57	0.043	0.116	0.05
With ascorbic acid	35	0.90			
II. Patients with rheumatic fever Initial values on entering hospital	17	0.59	0.087	0.19	0.03
III. Patients with rheumatic heart Initial values on entering hospital	26	0.62	Same as control group		0.00

* The control group was 110 children from Spalding School with no infectious disease and from about the same economic level as the patients.

I. Patients with scarlet fever were from the Municipal Contagious Disease Hospital.

II. Patients with rheumatic fever were from the Children's Memorial Hospital.

III. Patients with rheumatic heart disease were from the Children's Memorial Hospital and La Rabida Jackson Park Sanitarium.

The plasma ascorbic acid values of the patients with scarlet fever receiving supplements of ascorbic acid rose to an average of 0.90 mg. per hundred cubic centimeters during the five to ten day period. The average value finally attained was 1.03 mg. per hundred cubic centimeters.

PATIENTS WITH RHEUMATIC INFECTIONS

In this group 61 children with rheumatic infections were studied. They were divided into the following subgroups: Seventeen patients had symptoms of rheumatic fever with no evidence of cardiac involvement; 26 children had acute rheumatic heart disease, evidenced by rapid pulse, physical findings of cardiac involvement and increased sedimentation rate; 16 children were convalescing from acute carditis, and therefore are classified as having chronic rheumatic cardiac involvement. At the time of the study this group showed no evidence of active infection. They were free from fever and had normal pulse and sedimentation rates, though they exhibited residual physical signs of cardiac damage. Included in this group were 2 patients with chorea, who showed no lesions of the heart. All patients were observed over a period of one to two months.

Patients with Acute Rheumatic Fever.—Children suffering from acute rheumatic fever without initial evidence of cardiac involvement were selected from the wards at the Children's Memorial Hospital in Chicago.[5] Nine of the 17 patients received a supplement of ascorbic acid; the remaining 8 served as a control group, receiving no ascorbic acid other than that contained in the regular diet. The average initial value of ascorbic acid in the blood for this entire group of patients was 0.59 mg. per hundred cubic centimeters, which is not significantly lower than the values for the normal control group. The 9 patients receiving additional ascorbic acid showed a rise in the level in the blood values within two or three days. The average of all ascorbic acid values determined for the children of this group while their diet was being supplemented was 1.31 mg. per hundred cubic centimeters. The average of the final values attained with the supplemented diet was 155 mg. In some of these patients the supplemental administration of ascorbic acid was later discontinued, after which the blood level dropped slowly but never reached the initial level on admission.

The average of all plasma ascorbic acid values for the 8 control patients while they were on the unsupplemented hospital diet was 0.88 mg. per hundred cubic centimeters. This figure is considerably above the average value for the normal control group, probably because of the excellence of the hospital diet as compared with that previously received at home. The average of the finally attained values was 0.97 mg. per hundred cubic centimeters. Clinically there was no difference between the control group and the group receiving supplementary doses of ascorbic acid. In none of these 17 children did cardiac complications develop.

5. Through the courtesy of Dr. Joseph Brennemann, Medical Director, the Children's Memorial Hospital.

Patients with Acute Rheumatic Heart Disease.—Children with acute rheumatic heart disease were also selected from the wards of the Children's Memorial Hospital. There were 26 in this group, most of whom had been in the hospital on an adequate diet for some time prior to the beginning of the study. Nineteen of these patients were used as a control group, and 7 received supplementary doses of ascorbic acid. The initial average blood ascorbic acid value for this entire group was 0.62 mg. per hundred cubic centimeters, which is the same value as that obtained for the normal control group. The average of all plasma ascorbic acid values determined for the 7 patients after their diets had been supplemented with ascorbic acid was 1.37 mg. per hundred cubic centimeters, while the average for the 19 control patients for the same period of time was 0.92 mg. per hundred cubic centimeters. The average of the finally attained values of the group receiving a supplement was 1.35 mg. per hundred cubic centimeters, and that of the control group was 1.01 mg. per hundred cubic centimeters. It is evident from these figures that the values for both groups ranged within or above the levels of the normal control group. The plasma ascorbic acid attained relatively high levels in all patients receiving supplements with a single exception. This patient was too ill to retain all of her medicament. She died while under observation.

Of the 19 control patients who received no supplementary ascorbic acid, all except 2 attained fairly high levels in the blood plasma. One of these patients was ill with pancarditis and finally died. In the other patient a lack of appetite restricted the intake of ascorbic acid in the food.

In a few of the patients in both groups there was a temporary depression of the plasma ascorbic acid value during an exacerbation of the infection. This drop in level was less pronounced in the children receiving the ascorbic acid supplements. Ascorbic acid in large doses, however, did not prevent recurring attacks of fever and pains in the joints. Four patients whose blood plasma levels were well above normal showed a recurrence of symptoms. It is doubtful that vitamin C, even in large doses, influenced the clinical course of these patients.

Patients with Chronic Rheumatic Heart Disease.—The following studies were made on children convalescing from rheumatic heart disease at the La Rabida Jackson Park Sanitarium in Chicago.[6] There were 16 patients in this group, 7 of whom received supplemental doses of ascorbic acid; the other 9 served as controls. The average of all plasma ascorbic acid values determined for the 9 patients who did not receive additional vitamin C was 0.24 mg. per hundred cubic centimeters. Of

6. Through the courtesy of Dr. Robert A. Black, Chief of Staff, the La Rabida Jackson Park Sanitarium.

this group 2 patients received 15 grains (0.97 Gm.) of iron daily. Their average plasma ascorbic acid value was 0.21 mg. per hundred cubic centimeters. In the 7 patients receiving additional vitamin C, the average value was 1.15 mg. per hundred cubic centimeters. By way of comparison, the average initial value in this group of patients with

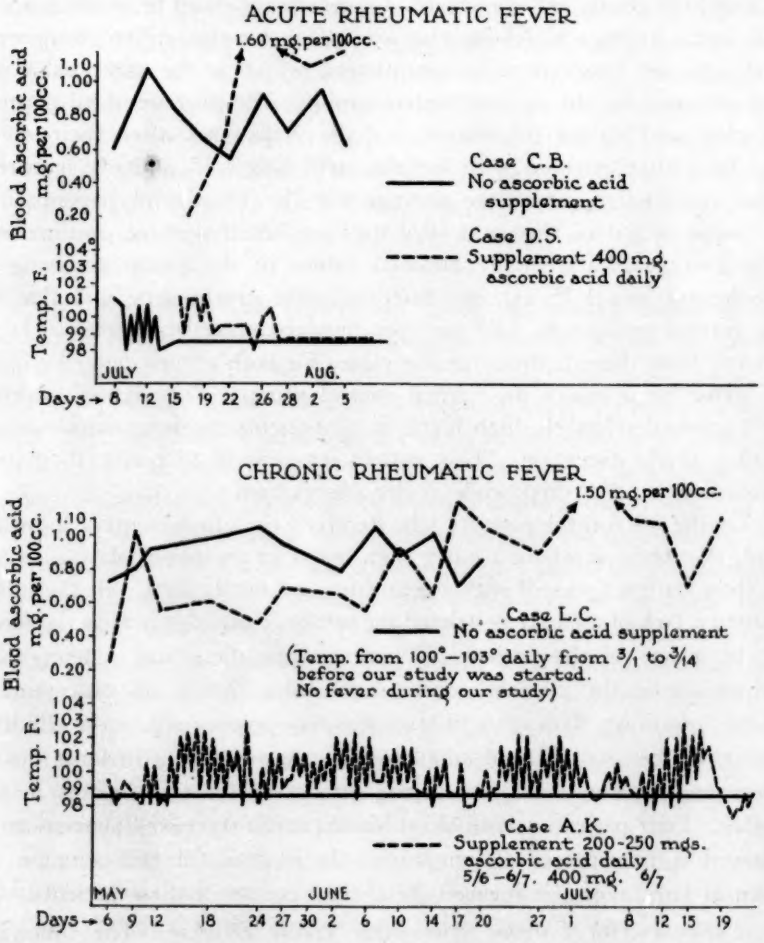

Chart 2.—Graphs of cases of acute and chronic rheumatic fever, showing the plasma ascorbic acid levels during the course of the illness.

chronic rheumatic heart disease was 0.38 mg. per hundred cubic centimeters, while for patients with acute rheumatic heart disease the average value was 0.62 mg. per hundred cubic centimeters. It was felt that this difference in plasma ascorbic acid values was probably due to the diet, since the group with the lowest values showed absolutely no evidence of active infection (chart 2).

Patients with Chorea.—Only 2 cases of Sydenham's chorea were obtained for study. One patient received additional doses of ascorbic acid and maintained a high level in the blood. The other received only the hospital diet. In this patient the plasma ascorbic acid level was normal on admission but dropped to subnormal during the hospital stay.

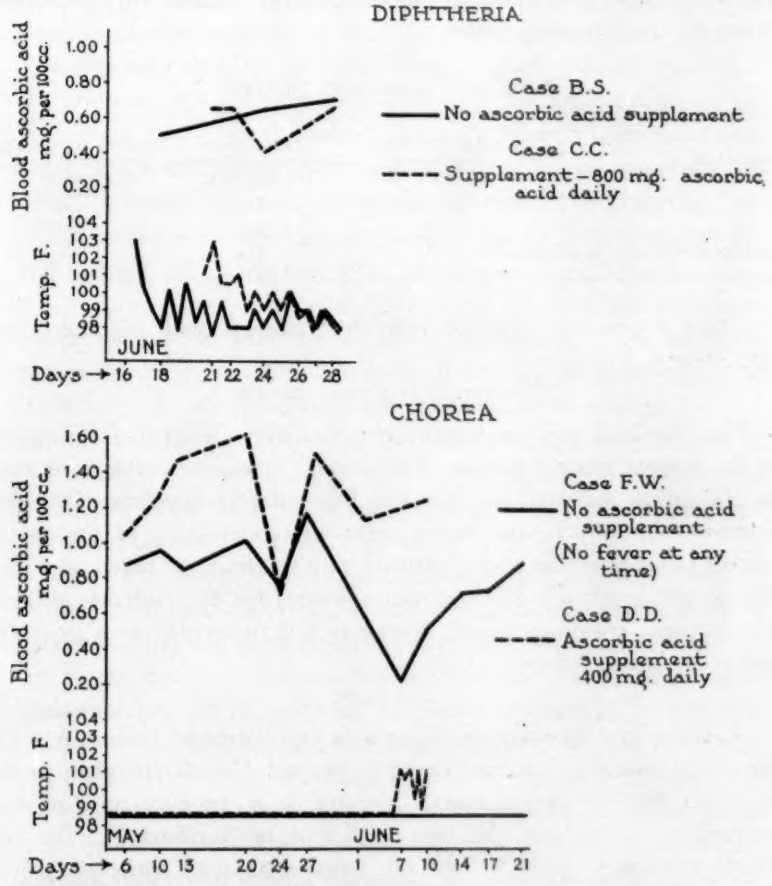

Chart 3.—Graphs of cases of diphtheria and chorea, showing the plasma ascorbic acid levels during the course of the illness.

Comment.—In summary, it is interesting to note that the average plasma ascorbic acid value of all patients in the aforementioned groups suffering with rheumatic infections who received ascorbic acid supplements was 1.28 mg. per hundred cubic centimeters. The average value for the patients with unsupplemented diets was 0.72 mg. per hundred cubic centimeters. The latter value is above the average value for the normal children of the control group.

PATIENTS WITH DIPHTHERIA

Eight patients with diphtheria were studied at the Municipal Contagious Disease Hospital, Chicago; 4 of these patients received supplemental doses of ascorbic acid and 4 served as controls.

The average initial plasma ascorbic acid value of the 8 patients and the initial and finally attained values of those receiving an ascorbic acid supplement and those serving as controls without supplement are shown in the following table:

TABLE 3.—*Patients with Diphtheria*

Number of Patients	Ascorbic Acid Supplement per Day, Mg.	Initial Value (Average of Group), Mg. per 100 Cc.	Finally Attained Value (Average of Group), Mg. per 100 Cc.
4	400 to 800	0.56	0.86
4	0	0.62	0.76
Average of 8 patients on entrance		0.59	

Chart 3 presents data for individual patients with diphtheria and with chorea.

NORMAL CONTROL GROUP

One hundred and ten healthy children were designated throughout as the normal control group. The average plasma ascorbic acid value for the group was 0.62 mg. per hundred cubic centimeters. The only average value which was significantly lower than that of the normal control group was that of the patients with scarlet fever taken on admission to the hospital. The low initial values for the patients suffering with chronic rheumatic heart disease is felt to be due to a poor diet and poor eating habits.

COMMENT

Relation of Vitamin C in General to Infection and Immunity.—The pathologic histology characterizing a vitamin C–deficient state as one in which the supporting tissues are unable to produce and maintain intercellular substances has been reviewed by Wolbach.[1d] The part which vitamin C plays in cellular metabolism may conceivably have a role in the maintenance of the natural resistance of the organisms to infection. According to Perla and Marmorston[1c]: "It is possible that changes in the resistance of scorbutic animals to infection are in part attributable to the altered permeability of membranes resulting from this change. That is, there is a breakdown in the normal protective capacity at the site of bacterial invasion of the body. This also suggests a decrease in the resistance of the tissue in general to injury of any type." And, finally, it can be readily assumed that there may be a greater demand for vitamin C during infection than in normal

states, if we assume that during infection metabolic cellular activity is increased. Harris, Passmore and Pagel [7] reported that guinea pigs suffering from an acute infection have shown a considerable diminution in the amount of vitamin C present in their adrenal glands as compared with control animals on the same intake of vitamins. The vitamin C content of the liver, however, was not reduced. In guinea pigs with a more chronic infection (tuberculosis) the vitamin C content of the liver was somewhat reduced as well as that of the adrenal glands. While these experiments are pertinent, there is again no positive evidence that the infected pigs absorbed the vitamin to the same extent as the normal animals, since fecal studies were not made; infection might conceivably cause a lessened absorption as well as an increased utilization. Further investigation is necessary to elucidate this problem.

Relation of Fever to Infection.—The exact role of fever in the utilization and metabolism of vitamin C is not known. Hasselbach,[8] from studies on patients suffering with pulmonary tuberculosis, concluded that during periods of fever the vitamin C requirements are increased and that in states of C avitaminosis an instability in heat regulation exists which can be alleviated by the administration of vitamin C.

Baumann and Rappolt,[9] studying the effects of various infections on the metabolism of vitamin C, state that in their opinion the height and duration of the fever seem to be the essential factors in the enhanced metabolism of vitamin C during infections.

In considering the utilization of ascorbic acid during fever, we maintain, at the outset, that one should clearly distinguish between a possible increased utilization due to an elevated body temperature and the utilization due to the infectious process per se. For these reasons we must be skeptical of reports of increased utilization of ascorbic acid during fever as due to the high temperature in experiments in which the temperature is induced by an infectious organism. Recently Rapaport [10] noted a pronounced increase in the level of vitamin C in the blood plasma of patients treated with hyperthermia. The plasma ascorbic acid returned to its approximate normal level in one hour after cessation

7. Harris, L. J.; Passmore, R., and Pagel, W.: Vitamin C and Infection: Influence of Infection on the Vitamin-C Content of Tissues of Animals, Lancet **2**:183 (July 24) 1937.

8. Hasselbach, F.: Vitamin C und Wärmeregulation, Schweiz. med. Wchnschr. **67**:877 (Sept. 11) 1937.

9. Baumann, T., and Rappolt, L.: Untersuchungen zum C-Vitaminstoffwechsel, Ztschr. f. Vitaminforsch. **6**:1 (Jan.) 1937.

10. Rapaport, H. G.: Effect of Hyperthermia on Vitamin C in Blood Plasma, J. Mt. Sinai Hosp. **6**:89 (July-Aug.) 1939.

of hyperpyrexia. Zook and Sharpless [11] studied the urinary excretion and blood plasma levels of ascorbic acid in 6 patients subjected to artificial fever. In 4 of these, less ascorbic acid was excreted into the urine during the day of treatment than on the previous or succeeding days. The maximum decrease in excretion in any patient was only from 23 mg. on the day prior to therapy to 10 mg. on the day of treatment. Loss of ascorbic acid by way of the sweat can be considered negligible.[12] They found no decrease in the plasma ascorbic acid level in any of their patients.

In a previous review [13] a preliminary report was given on the influence of artificial fever on the plasma ascorbic acid level of 18 patients with noninfectious arthritis. Seventy-seven treatments were given. The temperatures were induced by means of high frequency currents. The patients were permitted to drink water or saline solution, and the blood was examined for changes in concentration by the falling drop method of Barbour and Hamilton.[14] These studies show that no significant differences occurred between the level of plasma ascorbic acid during the fever and the pretreatment level. Some patients may show differences during a single treatment, but these differences are not constant in other treatments. The changes in specific gravity of the blood are not significant.

From the foregoing observations, the evidence seems to indicate but little or no effect of high temperatures on the level of ascorbic acid in the blood plasma. Urinary excretion, as observed by Rapaport, does not seem to be greatly decreased, since the pretreatment excretion was relatively low. In contrast, the decrease in the plasma ascorbic acid level shown during postoperative infection is pronounced.[9]

We conclude from our studies that high temperatures per se do not significantly lower the ascorbic acid content of the plasma or increase to any great extent the utilization of ascorbic acid in the body. Fever accompanied by active infection, as illustrated by the patients with scarlet fever, may increase the utilization of vitamin C, which is reflected by a decrease in the plasma level and in the urinary excretion.

Relation of Vitamin C to Scarlet Fever.—We chose scarlet fever as a disease for a comparative study with acute rheumatic fever because it is a febrile disease of relatively short duration, because a considerable

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11. Zook, J., and Sharpless, G. R.: Vitamin C Nutrition in Artificial Fever, Proc. Soc. Exper. Biol. & Med. **39**:233 (Nov.) 1938.

12. Wright, I. S., and MacLenathen, E.: Excretion of Vitamin C in Sweat, J. Lab. & Clin. Med. **24**:806 (May) 1939.

13. Farmer, C. J.: Vitamin C Analysis in Relation to Clinical Problems, Quart. Bull. Northwestern Univ. M. School **14**:220, 1940.

14. Barbour, H. G., and Hamilton, W. F.: Falling Drop Method for Determining Specific Gravity, J. Biol. Chem. **69**:625 (Aug.) 1926.

number of cases were available for study and, finally, because the etiologic agent of scarlet fever, the streptococcus, has occasionally been listed as the cause of rheumatic fever.

Few, if any, reports occur in the literature concerning studies on the metabolism of vitamin C in patients with scarlet fever. There are a few reports on the relation of vitamin C to infections of the upper respiratory tract. Alfred Hess [15] noted that a lack of vitamin C may induce susceptibility to infection of the respiratory tract. He believed that susceptibility may exist even before scorbutic signs are manifest, that is, in the "prescorbutic stage" or in "latent scurvy." He further stated that a local susceptibility without appreciable loss of systematic immunity may result from a low intake of vitamin C.

Abassy, Harris, Ray and Marrack [2a] have noted a diminished excretion of vitamin C in a patient with a mild coryzal fever. Baer [16] also noted a decreased excretion of vitamin C in studying cases of acute pharyngitis. Hetler,[17] in studying patients suffering with persistent chronic nasal sinusitis and chronic otitis media, observed a decreased amount of vitamin C in the blood plasma and urine. She stated that more vitamin C is needed to increase the level in the blood plasma in persons suffering from chronic infection than in normal persons. One patient was reported in whom an increased level of vitamin C in the blood occurred after intravenous therapy following an unsuccessful attempt to raise the level by oral administration of the vitamin. She further reported that the condition of the nasal mucous membrane was improved in patients suffering with chronic nasal disease after the concentration of vitamin C in the blood had been increased and maintained at a high level for several months by an increased intake of the vitamin.

Kaiser and Slavin [18] investigated the incidence of hemolytic streptococci in the tonsils of children as related to the vitamin C content of the tonsils and the blood. From their investigation they found a higher incidence of streptococci in the tonsils of the children who had the lower ascorbic acid values of blood and tonsils. These authors further performed virulence tests on the streptococci isolated from the tonsils and noted not only that streptococci are less likely to be found in the tonsils of children who have high blood ascorbic acid values but also that

15. Hess, A. F.: Diet, Nutrition and Infection, Acta pædiat. **13**:206, 1932.

16. Baer, M.: Ist die Pharyngitis eine C-Hypovitaminose? Deutsche med. Wchnschr. **63**:741 (May 7) 1937.

17. Hetler, R. A.: Study of Nutrition in Relation to Infections of the Upper Respiratory Mucous Membranes, Ann. Otol., Rhin. & Laryng. **46**:629 (Sept.) 1937.

18. Kaiser, A. D., and Slavin, B.: Incidence of Hemolytic Streptococci in Tonsils of Children as Related to the Vitamin C Content of Tonsils and Blood, J. Pediat. **13**:322 (Sept.) 1938.

the streptococci isolated from such children are seldom virulent. These authors concluded that, while a high level of ascorbic acid in the blood decreases the incidence of hemolytic streptococci likely to be found in the tonsils, it is also possible that infection of the tonsils may cause a lowering of the ascorbic acid in the blood.

We have observed the influence of an acute infection of the upper respiratory tract in a subject whose blood level and urinary excretion of vitamin C were followed over a period of two months. The subject, on leaving the customary diet and assuming a vitamin C–free diet, decreased the daily urinary excretion of ascorbic acid from 12.9 mg. with a blood level of 1.42 mg. per hundred cubic centimeters to a level of 6.7 mg. and a blood level of 0.47 mg. per hundred cubic centimeters in seven days. At this time he was given a daily dose of 20 mg. of ascorbic acid and established a blood level remaining constantly between 0.52 and 0.54 mg. per hundred cubic centimeters. The urinary excretion ranged between 7 and 9 mg. per day. On the day following the grippal attack, the daily urinary excretion dropped to 3.25 mg., while the blood level remained at 0.52 mg. per hundred cubic centimeters. As the temperature returned to normal, the urinary excretion was again restored to a value of 7.5 mg. per day, with a blood level still maintaining 0.54 mg. per hundred cubic centimeters.

Relation of Vitamin C to Rheumatic Fever.—Interest in the relationship of vitamin C to rheumatic fever commenced in 1933 with the experimental work of Rinehart and Mettier.[2b,c,d] These authors presented data from experiments on guinea pigs which led to the conclusion that rheumatic fever may be the result of the combined influence of vitamin C deficiency and infection. Prior to these publications Erdheim[19] recognized that cardiac hypertrophy and dilatation occur in children who die of scurvy, and he termed this type of heart Barlow *Herz*. He attributed the hypertrophy to difficulties in respiration caused by scorbutic changes at the costochondral junction. According to Isaac A. Abt,[20] while the early observers did not note clinical changes in the heart in scurvy, more recent observers[21] have detected enlargement clinically at the bedside, and this discovery has been confirmed by roentgen examination.

Recently Taylor[22] noted such pathologic conditions as valvulitis, myocarditis and occasionally pericarditis in guinea pigs suffering with

19. Erdheim, J.: Ueber das Barlow Herz, Wien. klin. Wchnschr. **31**:1293, 1918.

20. Abt, I. A.: Child's Heart in Avitaminosis, Am. J. Dis. Child. **50**:455 (Aug.) 1935.

21. Hess, A. F.: Scurvy, Past and Present, Philadelphia, J. B. Lippincott Company, 1920.

22. Taylor, S.: Scurvy and Carditis, Lancet **1**:973 (April 24) 1937.

scurvy. He concluded that vitamin C can prevent such lesions in guinea pigs but does not cure them. Perry,[23] using the urinary excretion test, concluded from studies on a small group of children that mild degrees of vitamin C deficiency are not uncommon in rheumatic children. Abbasy, Hill and Harris,[24] studying a larger group, noted a striking difference between the range of the urinary excretion of active and convalescent rheumatic patients and that of controls. These authors felt that their results indicated that in rheumatic subjects there is an increased need for vitamin C and possibly an increased destruction of the vitamin in the body. Faulkner [25] noted a slight increase of reticulocytes after administration of vitamin C to children suffering with rheumatic carditis, but he observed no clinical improvement in his patients. Sendroy and Schultz,[26] using the urinary excretion test, concluded that deficiency of vitamin C is not a predisposing factor in the causation of rheumatic fever, and further investigation by Schultz [27] led him to conclude that vitamin C, administered orally or intravenously, was not of therapeutic value in the treatment of acute rheumatic fever. Parsons [28] has repored a study of the urinary excretion of 18 children with acute rheumatism and 31 convalescent rheumatic children. In comparing the urinary excretion of ascorbic acid of the rheumatic group with that of a control group of nonrheumatic children, he noted, strangely, that the excretion of patients with acute rheumatism was greater than the excretion of the contro! group. It is assumed that the children in the control group received as much vitamin C in the diet as those with infection. Rinehart, Greenberg and Christie [29] studied the blood plasma levels of ascorbic acid and the urinary excretion in 21

23. Perry, C. B.: Rheumatic Heart Disease and Vitamin C, Lancet **2**:426 (Aug. 24) 1935.

24. Abbasy, M. A.; Hill, N. G., and Harris, L. J.: Vitamin C and Juvenile Rheumatism, with Some Observations on Vitamin C Reserves in Surgical Tuberculosis, Lancet **2**:1413 (Dec. 12) 1936.

25. Faulkner, J. M.: Effect of Administration of Vitamin C on Reticulocytes in Certain Infectious Diseases: Preliminary Report, New England J. Med. **213**:19 (July 4) 1935.

26. Sendroy, J., Jr., and Schultz, M. P.: Studies of Ascorbic Acid and Rheumatic Fever: Quantitative Index of Ascorbic Acid Utilization in Human Beings and Its Application to Study of Rheumatic Fever, J. Clin. Investigation **15**:369 (July) 1936.

27. Schultz, M. P.: Studies of Ascorbic Acid and Rheumatic Fever: Test of Prophylactic and Therapeutic Action of Ascorbic Acid, J. Clin. Investigation **15**: 385 (July) 1936.

28. Parsons, L. G.: Nutrition and Nutritional Diseases: Role of Vitamin C in Disease, Lancet **1**:123 (Jan. 15) 1938.

29. Rinehart, J. F.; Greenberg, L. D., and Christie, A. U.: Reduced Ascorbic Acid Content of Blood Plasma in Rheumatic Fever, Proc. Soc. Exper. Biol. & Med. **35**:350 (Nov.) 1936.

patients with acute rheumatic fever and noted the blood plasma levels to be almost uniformly lower than control values. In a more recent communication Rinehart, Greenberg, Olney and Choy [30] further confirmed these results and noted that not only in active rheumatic fever but in interval or inactive phases of the disease a state of subnutrition in regard to vitamin C exists. These authors postulated that the depletion of vitamin C in these patients probably resulted from inadequate intake or from depletion by the disease itself or by an inherent acquired metabolic fault. They further noted that the blood plasma levels of vitamin C in rheumatic fever are significantly lower than in a group of other miscellaneous infections. In a recent review Perla and Marmorston [1b] pointed out that "prolonged insufficiency of the vitamin may irreparably injure the organism to a point at which restoration of the normal state may never occur." They further noted that "it is possible that, once a rheumatic infection is established, the restoration of normal availability of vitamin C will not affect the carditis or prevent recurrences of the infection which is entrenched in the organism."

Kaiser [31] determined the vitamin C values in the whole blood of 13 children with acute rheumatic fever and of 12 children with chronic rheumatic fever. He noted that the levels of vitamin C in the whole blood of rheumatic children were somewhat lower than levels in a group of normal children whom he used for controls. However, in a group of children suffering from other acute febrile diseases, such as pneumonia, nephritis and tonsillitis, the values in the whole blood were also found to be lower than in the normal control group. Kaiser felt that there was sufficient evidence to conclude that it is important to include adequate amounts of vitamin C in the diets of all persons suffering from rheumatic disease.

Relation of Vitamin C to Diphtheria.—Earlier observers [32] reported a neutralizing effect of vitamin C on diphtheria toxin in vitro and in vivo. Sigal and King [33] were unable to confirm the reports of the detoxifying effect of the vitamin in vitro, with the exception of a nonspecific action, due to its acid character. They further state that the

30. Rinehart, J. F.; Greenberg, L. D.; Olney, M., and Choy, F.: Metabolism of Vitamin C in Rheumatic Fever, Arch. Int. Med. **61**:552 (April) 1938.

31. Kaiser, A. D.: Rheumatic Infection: Is Vitamin C Deficiency a Factor? New York State J. Med. **38**:868 (June 1) 1938.

32. (*a*) Jungeblut, C. W., and Zwemer, R. L.: Inactivation of Diphtheria Toxin in Vivo and in Vitro by Crystalline Vitamin C (Ascorbic Acid), Proc. Soc. Exper. Biol. & Med. **32**:1229 (May) 1935. (*b*) Greenwald, C. K., and Harde, E.: Vitamin C and Diphtheria Toxin, ibid. **32**:1157 (April) 1935.

33. Sigal, A., and King, C. G.: Vitamin C and Diphtheria Toxin, J. Pharmacol. & Exper. Therap. **59**:468 (April) 1937.

method of detoxification in vivo is probably due to the better nutritional level of the animals, rather than to direct chemical reaction of the vitamin on the toxin. In a later report [34] they noted that the level of vitamin C intake for optimum detoxification of diphtheria toxin in vivo is considerably greater than that necessary to protect from scurvy or to produce a favorable rate of growth. Ebel and Mautner [35] report that some agents accentuate the effect of diphtheria toxin while others have a detoxifying effect. Insulin belongs to the former group, while adrenal cortex and vitamin C belong to the latter. Pakter and Schick [36] administered large doses of ascorbic acid orally, intravenously, intramuscularly, subcutaneously and intracutaneously to children who had had positive reactions to the Schick test, after which they were again given this test at varying intervals. The positive reactions of these children to the Schick test were unaltered by the previous administration of vitamin C. These authors note that von Groer,[37] after studying the influence of p_H on the toxicity of diphtheria toxin, reported that the toxicity of toxin is changed by the p_H. They state that the toxin is probably not destroyed but changed into an atoxic form when acid is added. They conclude that any neutralizing effect which vitamin C may have is due to a nonspecific inactivation of the toxin through changes in the p_H due to the acidic nature of vitamin C. In a recent report Jungeblut [38] stated: "Neither vitamin C nor vitamin B_1 have any demonstrable effect in the development or the course of postdiphtheric paralysis in guinea pigs."

Otto,[39] in a study of 42 patients receiving vitamin C in addition to serum, noted improvement in the clinical condition of some patients. Ascorbic acid was administered intravenously in 500 mg. doses and also a 10 per cent solution was sprayed into the pharynx. This author abstained from oral administration, because, as he stated, ascorbic acid is destroyed by bacteria in the digestive tract. Following this line of reasoning, spraying the pharynx with a 10 per cent solution would hardly seem logical.

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34. Sigal, A., and King, C. G.: The Influence of Vitamin C Deficiency upon the Resistance of Guinea Pigs to Diphtheria Toxin: Glucose Tolerance, J. Pharmacol. & Exper. Therap. **61**:1 (Sept.) 1937.

35. Ebel, A., and Mautner, H.: Experimentelle Beiträge zur Therapie der Diphtherie, Wien. klin. Wchnschr. **49**:464 (April 10) 1936.

36. Pakter, J., and Schick, B.: Influence of Vitamin C on Diphtheria Toxin, Am. J. Dis. Child. **55**:12 (Jan.) 1938.

37. von Groer, F.: Diphtherietoxinstudien über den Einfluss der Wasserstoffionenkonzentration auf das Diphtherietoxin, Biochem. Ztschr. **138**:13, 1923.

38. Jungeblut, C. W.: Studies on the Inactivation of Diphtheria Toxin by Vitamin C (*l*-Ascorbic Acid), J. Infect. Dis. **69**:70 (July-Aug.) 1941.

39. Otto, H.: Die Behandlung der Diphtherie mit Ascorbinsaure, Klin. Wchnschr. **15**:1510 (Oct. 17) 1936.

Kumagai and co-workers [40] reported in 1937 that since 1936 they had supplemented the use of diphtheria antitoxin in the treatment of necrotic diphtheria by the injection of 400 to 600 mg. of ascorbic acid daily. Supplementary administration of epinephrine is recommended by these authors. Berger,[41] on the other hand, noted no influence of ascorbic acid and adrenal cortex extract on diphtheria intoxication. Further clinical experience is necessary to evaluate these conflicting reports. In suggesting any new therapeutic treatment for diphtheria, the established use of diphtheria antitoxin should never be overlooked or forgotten.

SUMMARY AND CONCLUSION

The data presented comprise a study of the relationship of vitamin C to the clinical course of scarlet fever, rheumatic infection and diphtheria in children. The clinical patients were divided into 6 groups, distributed as follows: 76 patients with scarlet fever, 17 with acute rheumatic fever not involving the heart, 26 with acute rheumatic heart disease, 16 convalescing from acute carditis, 2 with chorea and 8 with acute pharyngeal diphtheria. A control group of 110 normal children of the same socioeconomic status as the patients were included in the study.

The initial values for ascorbic acid in the blood plasma of the patients with scarlet fever were signficantly lower than the values of the normal control group. The clinical course, as noted from the tabulation of complications, was not influenced by the administration of relatively large oral doses of ascorbic acid.

In the other groups of patients—those with rheumatic fever, chorea and diphtheria—the initial plasma ascorbic acid levels were not significantly different from those of the normal control group. Though the patients given supplementary ascorbic acid did attain higher plasma levels than did those on the unsupplemented diets, we feel that the course of the diseases was not affected by large supplements of ascorbic acid. Finally, we may conclude from our studies that high temperatures per se do not significantly lower plasma ascorbic acid or increase to any great extent its utilization in the body. Fever accompanied by active infection, as illustrated by the group of patients with scarlet fever, may increase vitamin C utilization, which is reflected by a decrease in the plasma level and urinary excretion.

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40. Kumagai, K.; Yamagami, S.; Nikai, Y., and Imai, S.: Ueber die Wirkung des Vitamin C bei nekrotischer Diphtherie, Klin. Wchnschr. **16**:897 (July 10) 1937.

41. Berger, E.: Die experimentellen Voraussetzungen einer Behandlung der Diphtherie mit Vitamin C und Nebennierenrindenhormon, Klin. Wchnschr. **16**:1177 (Aug. 21) 1937.

MECONIUM ILEUS ASSOCIATED WITH STENOSIS OF THE PANCREATIC DUCTS

A CLINICAL, PATHOLOGIC AND EMBRYOLOGIC STUDY

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The association of inspissation of meconium in the newborn resulting in obstruction of the intestine (meconium ileus) and cystic fibrosis of the pancreas was first reported by Landsteiner,[1] in 1900. Kornblith and Otani [2] in 1929, by many serial sections of the pancreas in a case of meconium ileus, demonstrated a marked stenosis of the duodenal end of the duct of Wirsung with extreme dilatation of the duct. These investigators concluded that the stenosis of the duct of Wirsung produced the changes in the pancreas and that these, in turn, caused absence of pancreatic secretion in the intestine with alteration of the meconium. The case reports of meconium ileus by Dodd [3] in 1936, Bronaugh and Lattimer [4] in 1940, Denzer [5] in 1941 and Sobel [6] in 1941 described cystic dilatation of the pancreatic ducts, but studies of the pancreas by serial sections were not performed. The occurrence of a second case of meconium ileus at the Mount Sinai Hospital, in which there were changes in the pancreas almost identical with those described by Kornblith and Otani, prompted the present investigation.

From the Department of Laboratories of the Mount Sinai Hospital, the Pediatric Service of Dr. Béla Schick and the Surgical Service of Dr. Harold Neuhof.

* Fellow of the Dazian Foundation.

1. Landsteiner, K.: Intestinal Obstruction Due to Inspissated Meconium; Pancreatitis, Zentralbl. f. allg. Path. u. path. Anat. **16**:903, 1905.

2. Kornblith, B. A., and Otani, S.: Meconium Ileus with Congenital Stenosis of the Main Pancreatic Duct, Am. J. Path. **5**:249, 1929.

3. Dodd, K.: Intestinal Obstruction Due to Meconium Ileus in a Newborn Infant, J. Pediat. **9**:486, 1936.

4. Bronaugh, W., and Lattimer, R. D.: Intestinal Obstruction from Inspissated Meconium, Am. J. Dis. Child. **60**:1371 (Dec.) 1940.

5. Denzer, B. S.: Meconium Ileus, Am. J. Dis. Child. **62**:1114 (Nov.) 1941.

6. Sobel, I. P.: Meconium Ileus, Am. J. Dis. Child. **62**:1114 (Nov.) 1941.

REPORT OF A CASE

A boy aged 24 hours was admitted to the hospital on May 16, 1941, with the history of absence of passage of meconium per rectum since birth and intermittent regurgitation of bile-stained fluid for twelve hours. There were no abnormalities during pregnancy, the mother's first, or during the birth of the child.

Examination.—The temperature was 98.6 F. and the weight 6 pounds and 14 ounces (3,118.45 Gm.). The infant was well developed, with no abnormalities except on abdominal and rectal examinations. The abdomen was moderately distended, soft and nontender; no peristaltic waves were visible. Some oval, elongated masses were palpable. On rectal examination an obstruction was encountered by the finger about 2 inches (5 cm.) from the anus.

Fig. 1.—Roentgenogram of the abdomen (without the use of a contrast medium), showing pronounced distention of the loops of jejunum.

The hemoglobin content was 17.5 Gm. per hundred cubic centimeters. There were 11,200 white cells, of which polymorphonuclears were 43 per cent and lymphocytes 52 per cent. The microscopic examination of the urine revealed it to be normal. The Wassermann reaction of the blood was negative.

Soon after admission barium sulfate was introduced per rectum. Roentgen examination revealed a small stream of barium reaching the level of the descending colon. There was considerable distention of the small intestine (fig. 1).

An intravenous infusion of 5 per cent dextrose in a sodium chloride solution was started. The obstructive manifestations continued, and operation was performed by one of us (E. E. A.).

Operation.—Operation was performed ten hours after admission (under anesthesia) through an 8 cm. right rectus incision. Brown, odorless fluid escaped from the peritoneal cavity. Greatly dilated loops of small intestine, bluish in color, presented in the operative field. Removal of these loops from the peritoneal cavity was necessary in order to visualize the site of obstruction. A volvulus of the jejunum, of about 360 degrees in a clockwise direction, was untwisted by 2 complete counterclockwise turns. The jejunum distal to the volvulus then filled partially with gas. The bluish discoloration of the bowel was also relieved.

Almost the entire ileum was found on the right side of the abdomen, forming a mass of coiled intestine about the size of a fist. The loops of intestine, measuring about 1 cm. in diameter, were completely filled with a mass of inspissated meconium. The collapsed colon was about 3 mm. in diameter. There was no evident atresia anywhere in the small intestine or in the ascending or transverse colon.

Course.—Fluids (5 per cent dextrose in physiologic solution of sodium chloride and blood plasma) were given by intravenous drip continuously during and after operation. For about thirty-six hours the infant's condition remained fairly good but the abdominal distention was only slightly relieved and no meconium was passed per rectum. Thereafter, there was pronounced increase in the abdominal distention, and the child died forty-four hours after operation.

Gross Examination at Autopsy.—An autopsy was performed four hours after death by Dr. Wachstein and Dr. Hurwitt. An abstract of the protocol follows:

The body was that of a well formed white boy, 78 hours of age, weighing 6 pounds and 14 ounces (3,118.45 Gm.). The face was livid, and postmortem rigidity had not set in. A dried segment of umbilical cord, 4 cm. long, with a ligature at its distal extremity, was present. The abdomen was distended and tympanitic. An 8 cm. right rectus incision was present in the midabdomen with the sutures in situ. The wound had been healing normally. When the peritoneal cavity was opened, greatly distended loops of jejunum were seen. Filmy fibrinous adhesions were present in the lower part of the abdomen (mainly in the left lower quadrant), agglutinating loops of small bowel to each other and to the parietal peritoneum. There was about 300 cc. of turbid brown fluid in the iliac gutters.

Pancreas: The pancreas was normal in size, shape and location. On section, the parenchyma was found to consist of pale grayish white tissue which cut with increased resistance. The pancreatic duct in the head of the pancreas could not be visualized. Wirsung's duct could not be probed at the papilla of Vater, and the opening of the duct of Santorini could not be identified.

Gastrointestinal Tract: The esophagus and stomach were not unusual. The pyloric ring was not thickened. The duodenum presented no abnormalities. A short distance from the ligament of Treitz the jejunum became tremendously dilated, and this dilatation continued to the proximal few centimeters of ileum. In the course of this dilated jejunum there were two sharp angulations. The serosal surface of the bowel was dull, purplish red, thickened and coated with fibrinous adhesions. The wall of the jejunum was thickened, and the mucosa appeared thinned. The contents of the jejunum consisted of viscous, mucoid, green, odorless meconium. The ileum measured about 1 cm. in diameter and on palpation seemed to be filled with dense material; the wall was thickened. When opened, the ileum was found to be completely occupied throughout its entire extent by a cast of inspissated, pale green, firm, putty-like meconium. This

extended to the ileocecal valve. By gentle probing on either side of the ileocecal valve, a narrow lumen could be demonstrated, through which a probe could be passed with some difficulty. The distal tip of the ileum was greatly swollen, and the distal centimeter of ileum actually appeared invaginated into the cecum, resembling an early intussusception. This invagination caused a sharp kink in the contour of the bowel at the ileocecal junction; however, patency could be established. No anomaly of the valve was found.[7] The appendix was not unusual. The mesentery of the small bowel was thickened. The mesenteric glands were moderately enlarged and soft. Beyond the ileocecal valve, the entire colon and rectum were about 3 mm. in width, were patent throughout and were empty except for a scant amount of colorless, glairy, mucoid secretion.

Remaining Organs: There was a small blood cyst (valvular hematoma) on the anterior leaflet of the mitral valve. Minute petechiae were present on the apposing surfaces of the pericardium, and there was a slight increase of serous pericardial fluid. The lungs showed congestion and focal atelectasis. The liver appeared normal. The gallbladder contained a small amount of golden yellow bile. The common duct was not dilated and was patent to the papilla of Vater. The spleen, kidneys and genitalia were not unusual. Both adrenal glands were large and soft. On section of the right adrenal, soft hemorrhagic material poured forth easily. The left adrenal revealed a more nearly normal architecture, with a pale yellow cortical rim surrounding a soft, semifluid, brown central area.

Histologic Examination.—Pancreas: Serial sections of the head of the pancreas were made at intervals of 8 microns apart, numbering over five hundred sections in all. The duct of Wirsung, narrow as it ran alongside the common duct near the duodenum, consisted of many small lumens embedded in fibrous tissue. The lumens became progressively smaller, the stenosis reaching a maximum 280 microns from the first point at which the duct of Wirsung could be distinguished from the choledochus. As the duct diverged from the common duct into the substance of the head of the pancreas, the lumens dilated slightly but again attained a condition of considerable stenosis at a distance of 1,184 microns along the tortuous course of the duct. Beyond this point the duct rapidly became greatly dilated and through the remainder of the head and body of the pancreas appeared as large duct spaces (fig. 2).

The opening of the duct of Santorini was identified in a duodenal fold immediately adjacent to the papilla of Vater. For a short distance from the duodenal opening the duct was enormously dilated. This dilated section, however, was short, coming to an abrupt termination at a distance of 716 microns from the duodenal opening along the tortuous course of the duct. Beyond this point there was a rapid increase in fibrous tissue, the duct becoming subdivided into a few small lumens and continuing as a small duct in the head of the pancreas. No communication between the ducts of Wirsung and Santorini was demonstrated. Throughout the pancreas the periductal fibrous connective tissue was greatly increased, and this was most severe in the regions of the most pronounced narrowing of the ducts.

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7. The pathologic change at the ileocecal junction can best be reconstructed as follows: Because of the obstruction to the inspissated meconium at this zone of physiologic narrowing, violent peristalsis was induced. The net result of these efforts to move the material onward was to impact it against the walls of the terminal portion of the ileum so forcibly as partially to invaginate the side nearest the cecum into the cecum.

The ducts were lined by columnar epithelium. They contained amorphous material consisting of desquamated epithelial cells, products of secretion and deeply eosinophilic-staining concretions. In some of the larger ducts there were a few polymorphonuclear leukocytes, and the periductal connective tissue in the region of these ducts showed a moderate degree of infiltration with small cells. Throughout the length of the pancreas the smaller, and even the intra-acinar, ductules were greatly dilated and surrounded by atrophic acini and fibrous tissue. These changes were not localized to discrete areas but could be seen throughout the entire cross

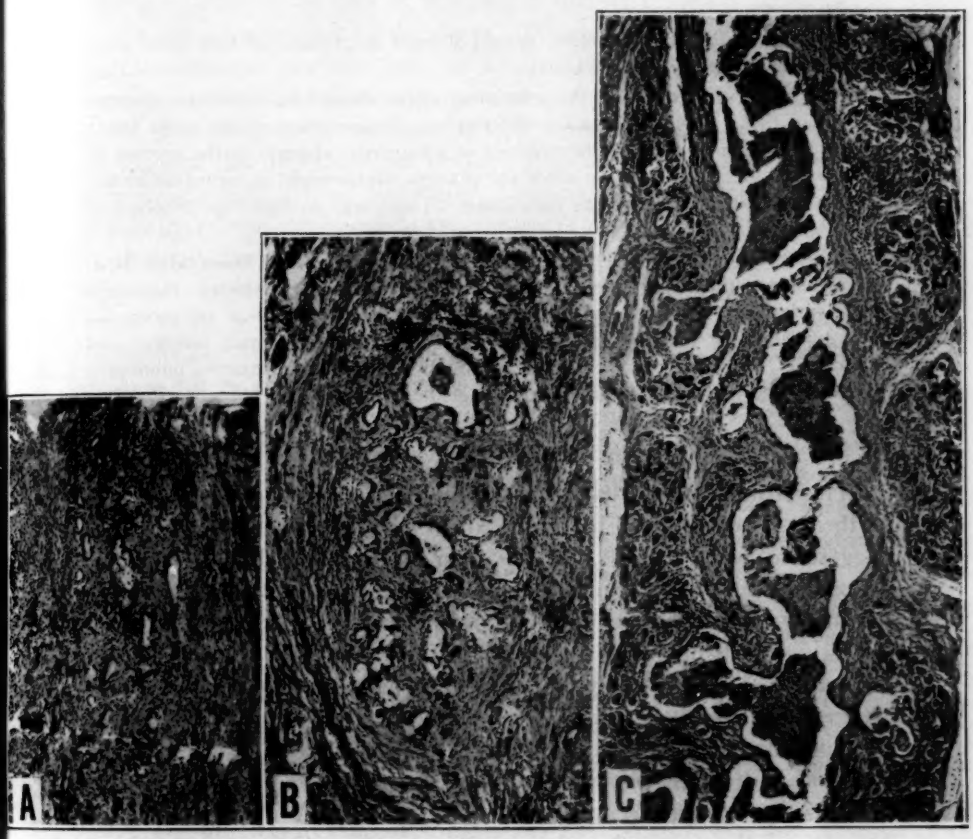

Fig. 2.—Sections of the duct of Wirsung (×46), showing: *A*, maximum narrowing; *B*, slight dilatation, and *C*, extreme dilatation at distances of 280, 440 and 3,600 microns respectively from the duodenal end of the duct.

section of the pancreas. Consequently, the architecture was completely distorted, and it was difficult to recognize even relatively normal areas for comparison. The islands of Langerhans showed early postmortem change, but their number and general architecture did not seem to be altered. The increase in fibrosis was particularly striking in the head of the pancreas. The fibrosis was distributed mainly in the periductal and interlobular fashion and did not involve the islets. The peripancreatic lymph nodes showed a slight increase in leukocytes.

Gastrointestinal Tract: The esophagus and stomach showed severe congestion of the submucosa. All of the sections of the small bowel revealed edema and congestion of the submucosa and subserosa. The mucosa of the jejunum was not unusual. In the ileum there was cystic dilatation of the mucosal glands. Throughout the small bowel there were distinct widening of the circular muscle and edema of the outer longitudinal muscle. The serosa was thickened, edematous, congested and in places coated with dark-staining amorphous material infiltrated with small round cells and histiocytes. Just proximal to the ileocecal valve, near the site of angulation, the lumen became definitely narrowed, but there was no evidence of atresia.

Umbilical Stalk: The umbilical vessels showed no changes of note other than a perivascular extravasation of blood.

Other Organs: Sections of the remaining organs showed no significant changes other than those noted in the gross description. Examination of the lungs failed to reveal any dilatation of the bronchioles or metaplastic changes in the mucosa of the bronchi. A search has been made for changes which might signify a deficiency of fat-soluble vitamins; none has been found. There was no histologic evidence of syphilis.

Pathologic Diagnoses: The pathologic diagnoses forty-four hours after laparotomy for intestinal obstruction and reduction of jejunal volvulus were: meconium ileus; fibrosis of the pancreas with stenosis and cystic dilatation of pancreatic ducts; pronounced hypertrophy of the muscular wall of the small intestine and dilatation of loops of jejunum; diffuse, acute, fibrinopurulent peritonitis; pulmonary congestion and focal atelectasis; blood cyst of the mitral valve.

PATHOGENESIS AND EMBRYOLOGY

The striking similarity of the pathologic changes in the pancreas in the case reported by Kornblith and Otani and in the present case suggests a common cause. It has been postulated that the pathologic changes in the pancreas in meconium ileus and pancreatic insufficiency in infancy can be classified into two main groups: (1) a group in which the primary changes are in the ducts (Kornblith and Otani, Oppenheimer), and (2) a group in which the changes are primarily in the parenchyma, the ducts being affected secondarily by the fibrous tissue.

The microscopic features observed in the pancreas in this case are identical with those described by Kornblith and Otani, except for the changes in the duct of Santorini. The stenosis of Wirsung's duct, the atrophy of the acini, the fibrosis and the preservation of the islets correspond in every respect. However, in their case the duct of Santorini was described as short, ending in the substance of the head of the pancreas, and showing no opening into the duodenum. No such extreme dilatation as that encountered in the present instance was described. In our case the excessive dilatation of the duct of Santorini near the duodenum with an abrupt transition to a stenotic condition was the reverse of the changes in the duct of Wirsung. The proximal dilatation of the duct of Santorini in our case might be explained as follows:

There was present a congenital stenosis of the duct of Wirsung with an extreme degree of dilatation of the intra-acinar ductules. This led to atrophy of the acinar tissue and subsequent fibrosis. The fibrosis involved the duct of Santorini secondarily, causing dilatation of that portion of the duct between the region of maximum fibrotic involvement and the opening of the duct into the duodenum. The striking resemblance of the changes in these 2 cases to those described as following experimental ligation of the duct of Wirsung is further evidence suggestive of a primary derangement of the ducts. Primary pancreatic parenchymal fibrosis does not produce such an extreme degree of dilatation of the distal portions of the ducts as is present in the 2 cases under consideration. The integrity of the islets of Langerhans in both cases also tends to support the hypothesis of primary disorder of the ducts; but this cannot be considered as conclusive, since in congenital syphilis, which primarily affects the parenchyma, the islets may or may not be intact.

Among the cases of pancreatic insufficiency in the newborn, there may well be a group in which the primary pathologic state will be found to be in the parenchyma of the pancreas. This would seem to be borne out by studies now in progress in other laboratories.[8] However, of the reported cases, even including those studied at autopsy, the ducts have been subjected to analysis by serial sections in very few instances. Even the most minute gross examination supplemented by a few random sections will not suffice in these cases. Conclusions should not be drawn when they are based on failure to probe the ducts of these newborn babies. We believe that a definitive statement cannot be made unless it is based on a study of serial sections.

We have discussed the reasons for considering the primary pathologic changes in the pancreas to be in the ducts, with secondary involvement of the parenchyma. The evidence for considering an inflammatory basis is very meager. The slight degree of infiltration of round cells in the fibrosed parenchyma, with no inflammatory reaction in the walls of the ducts themselves, is very inconclusive. Definite evidence of a specific infection is completely lacking.

There are features about these cases that suggest that the disease dates back to early intrauterine life. Only by a process of relatively long duration can such an extensive degree of pancreatic fibrosis be explained. In the case of Kornblith and Otani there was no meconium beyond the hepatic flexure of the colon; meconium was not found distal to the ileocecal valve in the present instance. In both cases the colon beyond the meconium was small in caliber and collapsed; the mucosa was pearly gray, translucent and unstained. Keith[9] stated that

8. Farber, S.: Personal communication to the authors.

9. Keith, A.: Human Embryology and Morphology, ed. 5, London, Edward Arnold & Co., 1933, p. 341.

meconium normally reaches the ileocolic junction in the fourth month and is present in the rectum of a 5 month fetus.

That a profound alteration of meconium dating probably from such an early intrauterine stage can be attributable to a deficiency of pancreatic secretions is a difficult postulate to prove. The theory that the fetal pancreas discharges an effective secretion into the duodenal lumen has both protagonists and antagonists. To quote from Frazer[10]: "Secretion, in the ordinary sense, does not take place in the embryonic pancreas, of course, but the early clearness of lumen in the growing structures seems to indicate that there is at least fluid present within these and entering the duodenum." Hess,[11] employing a duodenal catheter, was able to demonstrate the presence of trypsin, steapsin and amylopsin in newborn infants prior to their being put to the breast. In his article can be found a summary of the results of previous investigators and their analyses of fetal organs and the meconium of newborn babies. Trypsinogen was found in the fetal pancreas by Ibrahim and Heidenhain.[12] How early the elaboration of effective ferments occurs can hardly be surmised.

The possibility that stenosis of the pancreatic ducts in these cases represents a developmental arrest deserves close scrutiny. Varying degrees of atresia and stenosis of the biliary tract and of the duodenum are not uncommonly encountered. In the course of normal embryonic development, the lumen of the gallbladder and the biliary duct system are occluded by an epithelial proliferation (Keibel and Mall[13]); varying stages of this are found in embryos of from 4.9 to 16 mm. The duodenum, which has a well defined round lumen in the 6.5 mm. embryo, is similarly occluded in the 10 mm. embryo; vacuolation occurs, and at the 30 mm. stage the vacuoles commence to become confluent, with reestablishment of a central lumen.[14] These occlusions have for the most part been attributed to mechanical factors, such as resistance exerted on the expanding epithelium by the surrounding mesenchyme. When atresia of the biliary system or of the duodenum is found in a newborn child, it is thought to represent an arrest of development at this early occluded stage.

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10. Frazer, J. E. S.: A Manual of Embryology, ed. 2, London, Baillière, Tindall & Cox, 1940, p. 388.

11. Hess, A. F.: The Pancreatic Ferments in Infants, Am. J. Dis. Child. **4**:205 (Oct.) 1912.

12. Ibrahim and Heidenhain, cited by Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1924, vol. 3, p. 21.

13. Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 410.

14. Keibel and Mall,[13] p. 382.

It would not be surprising, therefore, if the pancreatic ducts, developing in the same region and subjected to the same mechanical factors, underwent a similar period of occlusion. A review of the literature on embryology failed to disclose any account of such a stage. Anomalies of the pancreas are rather rare and for the most part consist of accessory lobes, areas of pancreatic tissue in adjacent organs and variations in the union of the dorsal with the ventral pancreas. The most common of the variations in configuration of the ducts is obliteration of the proximal end of the duct of the dorsal pancreas, a malformation which is reported to be not infrequent (Keibel and Mall [15]). Baldwin [16] described variations in the relative amounts of pancreatic tissue drained by the two ducts, in the anastomoses between them and in the duodenal papillae; Bodinier [17] also cited an example in point. However, these anomalies are very infrequent and are in no way pertinent to the present consideration.

In an attempt to determine whether or not the pancreatic ducts follow a developmental pattern similar to that of the biliary tract and of the duodenum, a review of embryologic material at the Department of Embryology (Baltimore) of the Carnegie Institution of Washington was undertaken by one of us (E. S. H.). Serial sections of the region including the pancreas were studied in 54 embryos, ranging in size from 3 to 48 mm. Both the dorsal and the ventral pancreas have been described in embryos of 3 and 4 mm.; they are usually considered to be fused by the time the embryo is 14 to 15 mm. (Lewis [18]). The ventral pancreas forms the lower part of the head and the uncinate process of the fully developed gland. The duct of the ventral pancreas becomes the terminal portion of the main pancreatic duct (Wirsung) and empties with the choledochus. The dorsal pancreas, nearer the pylorus, forms the upper part of the head and the remainder of the bulk of the pancreas. The duct of the dorsal pancreas (Santorini) drains only a small portion of the head, the rest of the gland draining by way of anastomoses with the duct of Wirsung. The distal part of the duct of Santorini commonly becomes obliterated (Keith [19]).

In our study the smallest embryo in which definite pancreatic ducts with well defined lumens could be seen was 6.4 mm. The 9 embryos ranging from 3 to 6.2 mm. contained pancreatic tissue, but definite ducts were not made out. In 45 embryos from 6.4 to 48 mm. in size,

15. Keibel and Mall,[13] p. 440.

16. Baldwin, W. M.: The Ductus Pancreaticus Accessorius in Man, Anat. Rec. **1**:66, 1907.

17. Bodinier, cited by Ballantyne, J. W.: Manual of Antenatal Pathology and Hygiene, New York, William Wood & Co., 1905, vol. 2, p. 537.

18. Lewis, F. T., cited by Keibel and Mall,[13] p. 432.

19. Keith,[9] p. 319.

the dorsal pancreatic duct was traced from its origin at the dorsal aspect of the duodenum throughout its course, and the ventral pancreatic duct was examined from its origin at the common bile duct near the duodenum. Variations in the exact locale of origin of the ducts were noted, depending on the degree of rotation of the intestine and the size of the embryo. Consequently, in the larger specimens the duct of the dorsal pancreas appeared to stem from the ventral aspect of the duodenum; the origin of the ventral pancreatic duct from the choledochus could be seen within the well developed duodenal wall. The ducts of the ventral and dorsal pancreases were patent at their origins and throughout the gland in all of these 45 embryos. Dr. Bremer [20] was kind enough to examine the embryos in the Harvard collection up to 40 to 50 mm. in size, and he also could find no sign of plugging in the main pancreatic ducts.

On the basis of these studies, it can be stated that in the course of normal development the pancreatic ducts do not pass through a period of occlusion by epithelial proliferation, such as has been described in the biliary system and the duodenum. This cannot be interpreted, however, as signifying that the stenosis of the main pancreatic duct in the case of Kornblith and Otani and in the case reported here is not a developmental arrest. Dr. Streeter [21] reviewed the material in our case and felt that the most probable explanation was that of a formative "focal defect." According to this concept, defective cell development at an early stage can occur in any part of the body, resulting in all sorts of malformations. If this involves an overt area of the body, it is immediately grossly apparent in manifestations such as amputated extremities and giant digits. On the other hand, if it occurs in a "silent" area, its presence may never be suspected. There is no reason why the pancreatic ducts should not be affected occasionally, and this would certainly explain the stenosis in these 2 cases.

COMMENT

This study supports the concept of Kornblith and Otani that a causal relationship exists between stenosis of the pancreatic ducts and meconium ileus. We accept the view of Farber [8] that the basic lesion in meconium ileus is interference with the passage of pancreatic enzymes into the duodenum, no matter what the cause. On this basis, Farber has suggested that the inspissated meconium might be washed from the bowel by way of an enterostomy or colostomy, pancreatic extracts or duodenal juice being used as a solvent. This suggestion seems to us to be of

20. Bremer, J. L.: Personal communication to the authors.
21. Streeter, G.: Personal communication to the authors.

value in the therapy of this uniformly fatal condition, since death is due to mechanical blockade of the intestinal lumen. Four infants have been treated by this method at the Boston Children's Hospital,[22] and the cleansing of the meconium from the intestinal tract was successfully performed in 3 of these cases. One child has remained well for a long period, and 2 infants died several months later of a chronic pulmonary infection. If the intestinal obstruction can be relieved in this way, the ultimate outlook will depend on the degree of pathologic changes in the pancreas. It would seem that the histologic alteration of the pancreas is not severe enough to produce an actual pancreatic insufficiency, since a similar picture can be seen in cases of extreme atrophy of the acinar tissue with marked fibrosis caused by carcinoma of the head of the pancreas of long duration or by complete ligation of the main duct in the experimental animal.

The association of cystic fibrosis of the pancreas and celiac disease has been established by Andersen.[23] Oppenheimer,[24] Benoit [25] and Parmelee [26] reported cases of cystic fibrosis of the pancreas associated with atresia of the pancreatic ducts in infants dying at the ages of 7 months to 4½ years. Our embryologic studies disprove the occurrence of congenital atresia of the pancreatic ducts, such as may persist in the biliary system. It must be pointed out that examination of the duct systems in these older infants cannot be expected to produce a true picture of the condition of the ducts at the time of birth. With the establishment of the extrauterine digestive processes, secondary changes may occur which make it difficult to evaluate the primary pancreatic status. Had a marked stenosis of the ducts been present at birth, we believe these infants would have succumbed to meconium ileus.

The possibility that some of the patients with celiac disease might at birth have passed a somewhat altered meconium, representing a lesser, nonfatal degree of the change found in the present instance, has been considered. Dr. Ella Oppenheimer [27] reviewed her notes on the delivery of her patients with celiac disease at the Johns Hopkins Hospital and could find no record of unusual meconium at birth.

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22. Ladd, W. E., and Gross, R. E.: Personal communication to the authors.

23. Andersen, D. H.: Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease, Am. J. Dis. Child. **56**:344 (Aug.) 1938.

24. Oppenheimer, E. H.: Congenital Atresia of the Pancreatic Duct with Cystic Fibrosis of the Pancreas, Arch. Path. **29**:790 (June) 1940.

25. Benoit, W.: Hyperinsulinism with Congenital Atresia of the Pancreatic Duct, Endokrinologie **16**:313, 1935.

26. Parmelee, A. W.: The Pathology of Steatorrhea, Am. J. Dis. Child. **50**: 1418 (Dec.) 1935.

27. Oppenheimer, E. H.: Personal communication to the authors.

SUMMARY

A case of meconium ileus associated with stenosis of the main pancreatic duct and cystic fibrosis of the pancreas is reported; this is the second case in the literature.

A histologic study of the pancreas by serial sections is presented.

Investigation of early embryos reveals that the pancreatic ducts, in contrast with the biliary ducts and the duodenum, do not pass through a stage of occlusion by epithelial proliferation.

The cause of congenital stenosis of the pancreatic ducts is a focal developmental defect.

The basic lesion in meconium ileus is assumed to be interference with the passage of pancreatic enzymes into the duodenum; the practical application of this concept to the therapy of meconium ileus is discussed.

The Carnegie Institution of Washington gave us an opportunity to review their embryos. Dr. Sadao Otani made the photographic preparations.

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VITAMIN E IN PROGRESSIVE MUSCULAR DYSTROPHY

FAILURE OF ORAL ADMINISTRATION IN FIFTEEN CASES

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Progressive muscular dystrophy is a disorder of muscle presumed to be due to some primary degenerative process within the muscle tissue itself rather than to be a disturbance secondary to a lesion of the nervous system. The term includes a number of variations in type; the affected muscles in many instances are enlarged (pseudohypertrophic) but in others are normal or even atrophic in appearance. The cause of the condition is unknown, but the hereditary and familial occurrence are noteworthy. As its name indicates, the disease is distinguished by progressive weakness of the skeletal musculature, making its appearance, as a rule, in early childhood. The progress is slow in some cases but usually is rapid, and the disease is often fatal in early life. Unpreventable deformities of the extremities frequently interfere with walking long before the actual loss of muscle power would prevent locomotion. The pathologic effects of the disease appear to be limited to muscle tissue; the fibers early show swelling followed by the appearance of vacuoles containing fat and the eventual replacement of the muscle substance by fat and fibrous tissue. Coincidental with these changes in muscle, the patient is observed clinically to go through the course of progressive muscular weakness.

No successful treatment for progressive muscular dystrophy is known. What appears to have been a very rational attempt at therapy was the feeding of aminoacetic acid. It had been observed that in certain muscular disorders, including dystrophy, creatine was excreted in the urine in abnormal amounts. It is known that creatine is an essential substance in muscle, taking part in the chemical reaction by which muscle is activated to contract. Analysis of the dystrophic muscle is reported to show that these tissues are deficient in creatine content,[1] as the muscle tissue apparently is unable to retain the essential substance

1. Reinhold, J. G.; Clark, J. H.; Kingsley, G. R.; Custer, R. P., and McConnell, J. W.: The Effects of Glycine (Glycocoll) in Muscular Dystrophy, J. A. M. A. **102**:261-267 (Jan. 27) 1934.

and it passes out into the urine. Although creatine may be found in the urine of most children, it is normally excreted in the form of its dehydration product, creatinine; and the metabolism of creatine may be measured by the amount of creatinine excreted. The administration of creatine by mouth to the patient with progressive muscular dystrophy is of no value, as it does not result in the storing of more creatine in the muscles. Aminoacetic acid, however, is one of the precursors of creatine and when fed to the patient will cause an increase of the creatine content of the muscle.[1] The administration of aminoacetic acid is noticed to cause, first, an increase in urinary creatine; but, with the continued feeding, the urinary creatine level falls, as the substance is presumably stored in muscle, and the child is noticed to undergo clinical improvement in muscle strength. The creatinine content of the urine, indicative of the behavior of creatine in the body, likewise rises in those patients successfully treated. The claims of the results of therapy with aminoacetic acid differed widely, and the treatment has now fallen into disrepute. It would appear that there was improvement in the majority of patients but that this was temporary, lasting three to four months, and that the child gradually returned to his previous condition. The foregoing summary of creatine metabolism has been presented because it would seem to give a workable means of determining the efficacy of any proposed form of treatment of progressive muscular dystrophy.

Beginning with a paper in 1928 by H. M. Evans and G. O. Burr[2] at the University of California, there have appeared studies on the effect of the experimental deprivation of vitamin E in the laboratory animal. Such animals acquire a peculiar paralysis and are found to have changes in the nervous system suggestive of those of human amyotrophic lateral sclerosis and changes in the muscles fairly characteristic of those of progressive muscular dystrophy.[3] The prophecy of the beneficial results to be expected from the administration of vitamin E was first put to clinical test by Bicknell in London,[4] who reported the improvement of 12 of 18 patients with progressive muscular dystrophy. Bicknell administered twice daily ½ ounce (14 Gm.) of dried fresh whole wheat germ, a ready source of vitamin E. From his observations he concluded that progressive muscular dystrophy is a deficiency disease. He stated that "the discovery of the importance

2. Evans, H. M., and Burr, G. O.: Development of Paralysis in the Suckling Young of Mothers Deprived of Vitamin E, J. Biol. Chem. **76**:273-297 (Jan.) 1928.

3. Einarson, L., and Ringsted, A.: Effect of Chronic Vitamin E Deficiency on the Nervous System and the Skeletal Musculature in Adult Rats, London, Oxford University Press, 1938.

4. Bicknell, F.: Vitamin E in the Treatment of Muscular Dystrophies and Nervous Diseases, Lancet **1**:10-13 (Jan. 6) 1940.

of vitamin E in the treatment of muscular and nervous diseases appears to be revolutionary" and that "it appears indeed to be one of the great advances in general medicine of the century."

There soon appeared reports of improvement following the administration of vitamin E to patients with amyotrophic lateral sclerosis,[5] with infantile paralysis[6] and with muscular dystrophy. The vitamin was administered in the form either of natural dried whole wheat germ or of its derived oil. In the later papers the synthetic substance alpha tocopherol acetate was reported to have been used. This may be administered by mouth or intramuscularly.

Since progressive muscular dystrophy is a hopeless disease, we thought it worth while to follow the work of Bicknell, and in April 1940, three months after the appearance of his paper, we began the treatment of 15 patients with progressive muscular dystrophy at the Michael Dowling School for Crippled Children. There were 13 boys and 2 girls in the group studied. These children were all well known to us, having attended the school for a varying number of years, and we were able to control the daily routine of the individual patient. Careful objective records of muscle strength were made before, and at intervals during, the course of treatment (table 1). The statements of the child, the parent and the school attendants concerning subjective changes were also carefully recorded at regular intervals. The entire study extended over a period of twenty-two months. We began by administering vitamin E in the form of cold-pressed wheat germ oil, giving 1 teaspoonful daily (vitamin E content equivalent to 5.5 mg. of alpha tocopherol). This would contain an amount of vitamin E about one and one-third times that given by Bicknell in the 1 ounce (28 Gm.) daily doses of dry wheat germ which had caused improvement in his patients. At the end of five and one-half months an inspection of our patients did not show the expected improvement. At that time we were able, however, to obtain a preparation of concentrated vitamin E (mixed natural tocopherols) in oil, and we began the administration to each child of a quantity of the vitamin concentrate equivalent to about 30 teaspoonfuls of wheat germ oil daily (vitamin E content equivalent to 156 mg. of alpha tocopherol). At the end of two and one-half months of therapy with the concentrate, we were further discouraged in finding no objective improvement in the patient. However, there

5. Wechsler, I. S.: Recovery in Amyotrophic Lateral Sclerosis Treated with Tocopherols (Vitamin E): Preliminary Report, J. A. M. A. **114**:948-950 (March 16) 1940.

6. Stone, S.: Treatment of Muscular Dystrophies and Allied Conditions: Preliminary Report on Use of Vitamin E (Wheat Germ Oil), J. A. M. A. **114**: 2187-2191 (June 1) 1940.

then came to our attention the report of Stone [6] that vitamin E was more efficacious when administered in conjunction with the vitamin B complex. We also became aware of the report of Antopol and Schotland [7] that vitamin B_6 would cause improvement in patients with

TABLE 1.—*Record of Condition and Progress of Each Child*

Observations of Child, Parent, and School Attendant Recorded on Reverse Side												
Date:												
Walks unaided												
Arises from chair: With aid of hands Without aid of hands												
Arises from supine position												
Mounts stairs: With aid of hand rail Without aid of hand rail												
Left							Right					
						Date						
						Shoulder Abduction forward Abduction sideward						
						Elbow Flexion Extension						
						Wrist Flexion Extension						
						Fingers Flexion Extension Palmar Interossei Dorsal Interossei						
						Trunk Head raising Supine to sitting						
						Hip Abduction Adduction Flexion Extension						
						Knee Flexion Extension						
						Ankle Dorsiflexion Plantar flexion						

Grading: (1) normal; (2) good; (3) fair; (4) poor; (5) trace; (6) 0.

progressive muscular dystrophy. We therefore, in addition to the administration of vitamin E, gave vitamin B_1 and vitamin B_6 in significant amounts daily (3 mg. of thiamine hydrochloride and 25 mg. of pyridoxine hydrochloride). An additional period of seven months of observation now followed, while the patients were on the combined

7. Antopol, W., and Schotland, C. E.: The Use of Vitamin B_6 in Pseudohypertrophic Muscular Dystrophy, J. A. M. A. **114**:1058-1059 (March 23) 1940.

vitamin regimen, but again results were negative. We concluded that, if we could have any belief in the report of Bicknell, there must be some substance in whole wheat germ not present in the wheat germ oil that is effective in curing progressive muscular dystrophy. We therefore decided to administer the dried fresh whole wheat germ, which was the preparation originally used by Bicknell. All patients were given the dry germ, receiving 2 ounces (56 Gm.) daily (vitamin E content equivalent to 8.5 mg. of alpha tocopherol), which was twice the amount recommended by Bicknell. All patients have continued this dosage during the seven months up to the time of writing present report. A complete summary of the medication given during the entire course of treatment is presented in table 2.

TABLE 2.—*Medication (All Oral)*

Date	Preparation	Dose
April 15 to Oct. 1, 1940	Wheat germ oil	1 teaspoonful daily (vitamin E content equivalent to 5.5 mg. of alpha tocopherol)
Oct. 1 to Dec. 15, 1940	Mixed natural tocopherols in oil	3 divided doses daily (vitamin E content of daily dose equivalent to 156 mg. of alpha tocopherol)
Dec. 15, 1940 to July 15, 1941	Mixed natural tocopherols in oil	Vitamin E content of daily dose equivalent to 156 mg. of alpha tocopherol
	Thiamine hydrochloride	1 tablet (3 mg.) daily
	Pyridoxine hydrochloride	1 tablet (25 mg.) daily
July 15, 1941 to Feb. 15, 1942	Dried fresh whole wheat germ	1 ounce (28 Gm.) twice daily (vitamin E content of daily dose equivalent to 8.5 mg. of alpha tocopherol)

The wheat germ oil, thiamine hydrochloride and dried fresh whole wheat germ (Embo) were supplied by General Mills, Inc., Minneapolis; the mixed natural tocopherols in oil (Vegol), by Distillation Products, Inc., of Rochester, N. Y., and the pyridoxine hydrochloride by Merck & Co., Inc., Rahway, N. J.

An analysis of our data during the total twenty-two months of treatment gives the following results in the 15 cases:

1. Of the fifteen patients, none was objectively improved. In all instances the disease progressed unretarded, as determined by tests of muscular strength. Five patients ceased to walk during the period of observation.

2. Subjectively, 5 subjects claimed improvement, in that they enjoyed better general health. These patients stated they did not tire as easily as they had and that they were more energetic in daily activities.

3. In 3 cases the mothers thought the disease was not as rapidly progressive as it had been prior to the beginning of medication.

The individual cases are summarized in table 3.

As a result of our observations over twenty-two months, we cannot but conclude that vitamin E when administered by mouth does not help patients with progressive muscular dystrophy. Other equally

negative reports are appearing in the literature. It seems difficult to reconcile these records of complete failure with the glowing claims of Bicknell and other observers.

The fate of the vitamin E which we gave is unknown to us. As it was all administered by mouth, it is possible that none of the vitamin

TABLE 3.—*Summary of Cases*

Patient	Sex	Age	Age at Onset	Type Appearance of Musculature	Condition on Beginning Treatment	Course and Result
1. B. S.	M	10	3	Hypertrophic	Rapidly progressive; still walking	Disease progressed unretarded; ceased walking one month after beginning treatment
2. C. M.	M	15	3	Hypertrophic	Slowly progressive; able to take a few steps	Ceased walking; general health improved; disease progressed unretarded
3. D. M.; cousin of 7 and 8	M	19	9	Normal size	Slowly progressive; walking	Disease progressed unretarded; general health better; did not tire as readily when under treatment
4. R. M.	M	15	4	Hypertrophic	Slowly progressive; walking	Disease progressed unretarded; did not tire as readily when under treatment
5. R. L.	M	10	1	Hypertrophic	Rapidly progressive; still walking	Disease progressed unretarded; ceased walking
6. G. J.	M	10	Birth	Hypertrophic	Slowly progressive; walking	Disease progressed unretarded; ceased walking
7. R. H.	M	18	5	Atrophic	Slowly progressive; not walking	Disease progressed unretarded; no advantageous effect from treatment
8. R. H.; brother of 7	M	12	4	Hypertrophic	Slowly progressive; walking	Disease progressed unretarded; no advantageous effect from treatment
9. W. D.	M	17	5	Hypertrophic	Slowly progressive; not walking	Progress of disease slowed
10. T. D.; brother of 9	M	14	5	Hypertrophic	Slowly progressive; not walking	Disease progressed unretarded; no advantageous effect from treatment
11. G. C.	M	8	5	Hypertrophic	Rapidly progressive; not walking	Disease progressed unretarded; no advantageous effect from treatment
12. W. B.	M	12	4	Hypertrophic	Slowly progressive; not walking	Progress of disease slowed
13. Mc. B.	M	17	3	Hypertrophic	Slowly progressive; not walking	Disease progressed unretarded; patient in better spirits when under treatment
14. J. L.	F	19	1½	Hypertrophic	Slowly progressive; walking	Progress of disease slowed; did not tire as easily
15. L. W.	F	16	4	Atrophic	Slowly progressive; walking	Disease progressed unretarded; ceased walking because of deformities

was absorbed. However, there are reports of failures with parenteral (intramuscular) injection of the vitamin and with combined administration. Recent studies of the effect of vitamin E on the creatine metabolism of patients with progressive muscular dystrophy [8] indicate that this

8. Fleischmann, W.: Creatine-Creatinine Excretion in Neuromuscular Diseases Treated with Alpha-Tocopherol and with Testosterone, Proc. Soc. Exper. Biol. & Med. **46**:94-96 (Jan.) 1941. Harris, M. M.: Negative Therapeutic and Metabolic Effects of Synthetic Alpha-Tocopherol (Vitamin E) in Muscular Dystrophy, Am. J. M. Sc. **202**:258-264 (Aug.) 1941.

metabolism is not influenced by the vitamin insofar as can be judged by the output of creatine in the urine. We made no attempt to evaluate this effect in our purely clinical study. There has been no reported work showing that the body lacks vitamin E in progressive muscular dystrophy. A recent report [9] states that the amount of vitamin E in the blood is normal in untreated amyotrophic lateral sclerosis, one of the diseases presumably also due to deficiency of vitamin E and alleged by some to be relieved by administration of the vitamin E.

Progressive muscular dystrophy still remains to us a progressive and incurable disease.

1945 Medical Arts Building.

9. Wechsler, I. S.; Mayer, G. G., and Sobotka, H.: Tocopherol Level in Serum of Normals and Patients with Amyotrophic Lateral Sclerosis, Proc. Soc. Exper. Biol. & Med. **47**:152-156 (May) 1941.

PERCUTANEOUS ADMINISTRATION OF VITAMIN K

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The conventional methods of administering vitamin K to the newborn infant are not ideal. Oral administration of oily solutions involves the danger of lipid pneumonia as well as of damage caused by the irritating naphthoquinones themselves. Parenterally injected oily solutions of synthetic vitamin K cause encapsulation of the oily depot and are slowly absorbed. This disadvantage has in part been overcome by the use of water-soluble derivatives. However, the irritant effect of the naphthoquinones remains. Moreover, an injection into a newborn infant should if possible be avoided.

Percutaneous administration of vitamin K would overcome all these disadvantages and popularize the general use of this preventive medium. It is true that this route of administration is incompatible with exact dosage. However, vitamin K seems generally to be so overdosed that even the loss of a material part of the usual 1 mg. dose would not be critical. Sells, Walker and Owen [1] showed that 0.001 mg. of synthetic vitamin K (menadione) is the minimum requirement for newborn infants. As is shown later, small fractions of a milligram are fully effective when administered percutaneously.

One drawback had to be anticipated for this form of application. Methylnaphthoquinone is known to be a primary cutaneous irritant. In fact, an ointment containing 1 per cent of menadione (2-methyl-1, 4-naphthoquinone) caused a burning sensation and an erythema to several adults following its topical application. Repeated administration of such an ointment to the same area of skin almost regularly caused disturbing cutaneous irritations.

These untoward effects were avoided by decreasing the concentration of menadione in the vehicle to 0.1 and 0.01 per cent; no cutaneous irritation ever resulted, even from repeated topical application of these

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From the Department of Obstetrics and the Department of Pediatrics of the Lincoln Hospital.

1. Sells, R. L.; Walker, S. A., and Owen, C. A.: Proc. Soc. Exper. Biol. & Med. **47**:441, 1941.

dilutions. On the other hand, the efficacy was questioned when such low concentrations of vitamin K were topically applied. This was compensated for by enhancing its percutaneous absorption.

The rate of percutaneous absorption of a drug is, among other factors, a function of the viscosity of the vehicle. High viscosity, such as is inherent in ointments, hampers absorption; low viscosity enhances it. Light liquid petrolatum, of the lowest viscosity, was used as a basic vehicle, and its viscosity was further diminished by adding to it hydrocarbons of low boiling point. Deodorized kerosene proved to be satisfactory for this purpose. Essential oils may also reduce the viscosity of oil, but their use is precluded, because they form peroxides and destroy methylnaphthoquinone by oxidation.

If increasing percentages of kerosene are added to liquid petrolatum, the reduction of its viscosity progresses in the form of a hyperbolic curve. Relatively small proportions of kerosene materially decrease the viscosity of liquid petrolatum. Eighty parts of liquid petrolatum and 20 parts of odorless kerosene were used as the solvent for menadione. This mixture is noninflammable, does not irritate the skin, is easily absorbed and keeps the synthetic vitamin K stable when stored in a brown or black bottle.

Concentrations of 0.01 to 1 per cent of menadione in this vehicle were used for percutaneous administration to the newborn infant. Exactly determined amounts of the vitamin-oil mixture, usually 0.1 cc., were applied to the chest of the infant and distributed over the skin by means of a metal spatula to avoid loss through application by hand. This precaution is not required for practical purposes.

METHOD

The micromethod described by Quick [2] and, independently, by Lawson [3] was used for the determination of the prothrombin time. Thromboplastin was prepared according to the directions of Quick from fresh rabbit brain, and the suspensions were stabilized with a thymol crystal. Twenty cubic millimeters of the thromboplastin suspension, measured in a Sahli hemoglobin pipet, was placed in the well of a hollow-ground slide. The same amount of blood, measured in a second hemoglobin pipet, was taken from a puncture in the infant's heel without squeezing and mixed with the thromboplastin for five seconds by means of a glass rod. The slide was tilted until the exact end point when clotting occurred, and the time from the addition of the blood to the moment of clotting was measured with a stopwatch. This simple bedside test, which does not require any special equipment, proved to be satisfactory. For every infant the first prothrombin test was done within twenty-four hours after delivery; in some cases this was during the second calendar day of life. This first determination always preceded the single percutaneous administration of menadione. Subsequent prothrombin tests were made at intervals of about twenty-four hours.

2. Quick, A. J.: Proc. Soc. Exper. Biol. & Med. **42**:788, 1939.

3. Lawson, R. B: J. Pediat. **18**:224, 1941.

RESULTS

Chart 1 shows the prothrombin times of 9 untreated newborn infants. These curves conform to those of other investigators, presenting maximum levels on the second or third day and spontaneously falling to normal prothrombin times between the fifth and the seventh day of life.

Chart 2 represents the prothrombin times of 7 infants to whom 1 mg. of menadione was percutaneously administered during the first

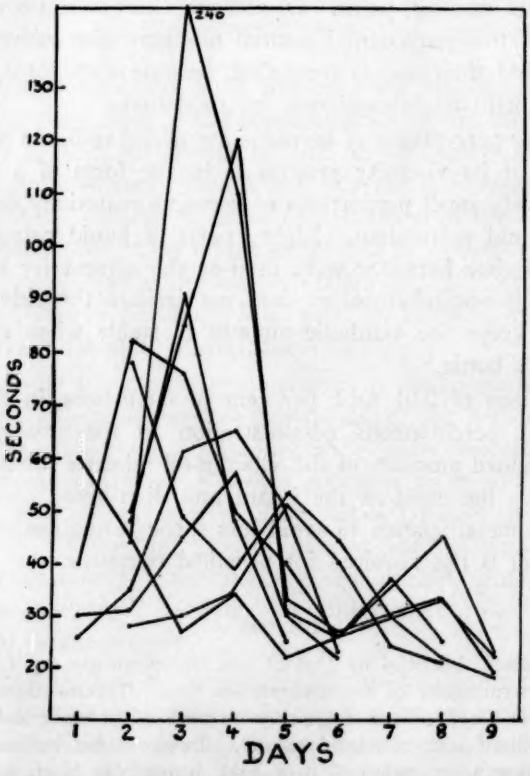

Chart 1.—Prothrombin times of 9 untreated newborn infants. The normal adult control time was eighteen to twenty-two seconds.

day of life immediately after the first blood test. All prothrombin times determined after the percutaneous administration of vitamin K were within normal range, indicating the full efficacy of this prophylactic procedure.

Chart 3 gives a "slow motion" analysis of the effect of the percutaneous administration of vitamin K to a newborn infant with clinical hemorrhagic disease of the newborn. The first prothrombin time was more than two hundred and forty seconds, and bleeding from the

umbilical stump and from multiple breaks in the skin occurred, accompanied by large hematoma of the buttocks and thighs and hematemesis. Immediately after this initial determination, 1 mg. of vitamin K in

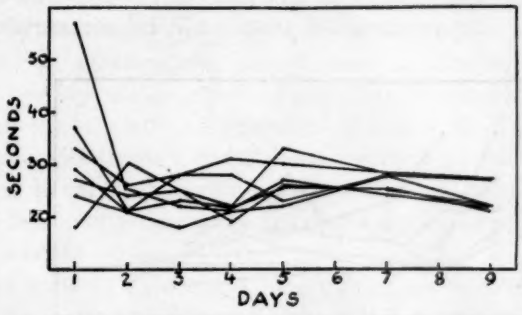

Chart 2.—Prothrombin times of 7 newborn infants who received 1 mg. of menadione percutaneously after the first determination.

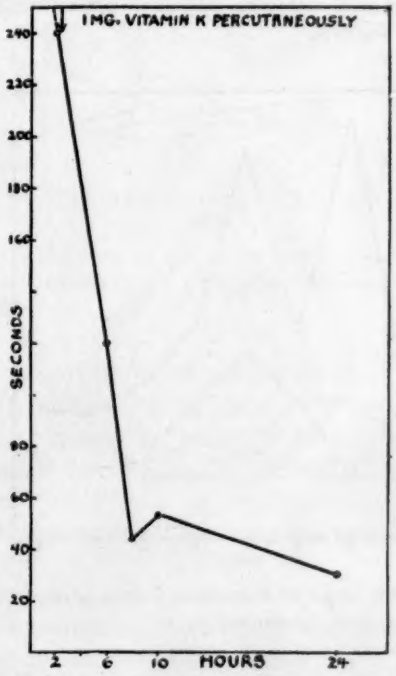

Chart 3.—Prothrombin times of a newborn infant with clinical hemorrhagic disease who was treated with percutaneous administration of 1 mg. of menadione. The bleeding ceased four hours after treatment.

oil was administered percutaneously. Four hours later the bleeding ceased, and the prothrombin time was one hundred and twenty seconds;

six hours after the inunction the prothrombin time was and remained normal. Hemorrhages did not recur.

Chart 4 demonstrates that the percutaneous administration of 0.1 mg. of menadione has about the same effect as the percutaneous administration of 1 mg. The prothrombin times of 7 infants remained within

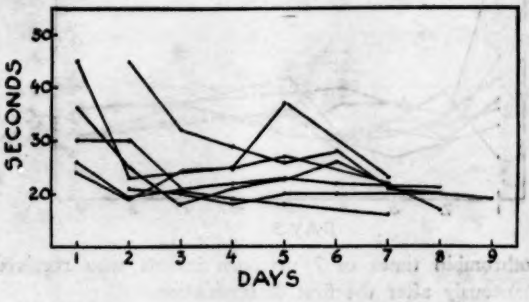

Chart 4.—Prothrombin times of 7 newborn infants given 0.1 mg. of menadione percutaneously after the first determination. The normal adult control time was nineteen to twenty-one seconds.

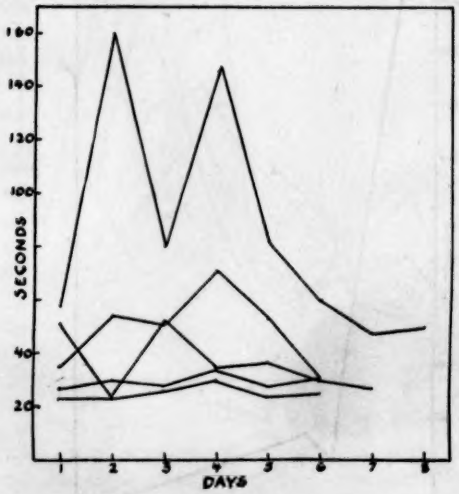

Chart 5.—Prothrombin times of 5 newborn infants given 0.01 mg. of menadione percutaneously after the first determination.

normal range. The full effect of such small doses could be interpreted in two ways. Either the percutaneous method if superior to the oral and subcutaneous methods of administration of vitamin K, or the conventional 1 mg. dose is far beyond the actual vitamin K requirement of infants. The proper explanation is given by the following experiments.

Chart 5 shows the prothrombin times of 5 infants who were given only 0.01 mg. of menadione percutaneously. This small dose proved

to be sufficient in 3 but insufficient in 2 cases. The minimum effective dose of menadione when administered percutaneously is therefore approximately 0.01 mg., but this dose is not sufficient for every infant. When the same dose, of 0.01 mg. of menadione, diluted in sesame oil, was given by mouth, it proved to be effective in all 5 infants, as shown in chart 6. In other words, higher doses of vitamin K seem to be required when percutaneously than when orally administered. This is in line with the theoretic expectations. Vitamin K is not absorbed in as large quantities through the skin as it is through the intestinal tract. On the other hand, the conventional oral and parenteral dose of 1 mg. of menadione is a luxury dose and exceeds the minimum requirement more than one hundred times.

Another series of experiments was carried out to determine whether the percutaneous administration of vitamin K to mothers during labor is feasible and will protect the infants from prothrombinopenia. One single dose of 1 or 2 mg. of menadione diluted in the liquid petrolatum–

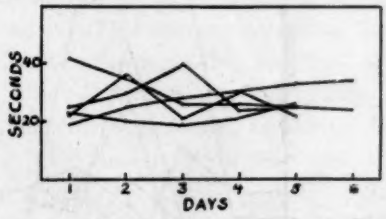

Chart 6.—Prothrombin times of 5 newborn infants given 0.01 mg. of menadione orally after the first determination. The normal adult control time was eighteen to twenty-one seconds.

kerosene solvent was administered percutaneously to the chest (between the breasts) of 15 mothers during labor. Cutaneous irritation did not result. The time between the administration of the vitamin and the delivery of the infant varied from twenty-two minutes to twenty hours and was expected to influence the results. Daily determinations of prothrombin time were made for the infants, the first within twenty-four hours after delivery.

Chart 7 demonstrates the prothrombin time curves of the infants in relation to the time intervals between the administration of vitamin K to the mother and the delivery of the infant. In this series of 15, only 3 infants had shown critical prothrombin times (above seventy-five seconds). The mothers of these infants received vitamin K percutaneously either more than fifteen or less than two hours before delivery. Prothrombin times between fifty and seventy-five seconds, which are not critical but are above normal, were encountered in the cases of 3 other infants whose mothers received vitamin K two hours or less

before delivery. Though no final conclusion is permissible from this small number of observations, the results suggest that mothers should receive vitamin K percutaneously from two to fifteen hours before delivery. Beyond this range protection of the infant is not assured. McCready, Callahan and Grandin [4] arrived at similar conclusions. Lawson [3] expressed the belief that an oral dose of 2 to 4 mg. of menadione in oil must be given to mothers at least five hours before delivery. In our series 3 mothers received a percutaneous dose of 2 mg. twenty-two, thirty and seventy minutes respectively before delivery, with resulting normal or slightly elevated prothrombin times in the infants. This seems to indicate that vitamin K is absorbed at least as quickly

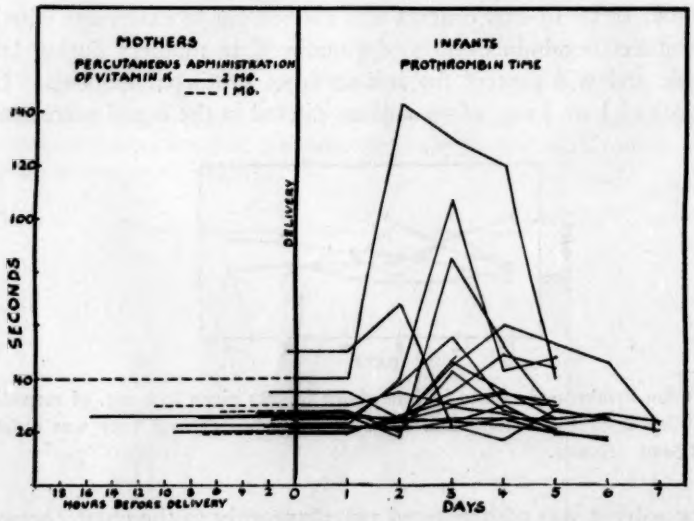

Chart 7.—Prothrombin times of 15 newborn infants whose mothers received 1 or 2 mg. of menadione percutaneously during labor. The intervals between the administration of the vitamin and delivery varied from twenty-two minutes to twenty hours and are shown on the left side of the chart.

when percutaneously as when orally administered. There was no appreciable difference between the effects of 1 and 2 mg. of vitamin K. Both doses seem to be beyond the minimum requirement when administered at the right time. Since the hour of delivery cannot be predicted, a single percutaneous administration of vitamin K to the mother cannot be regarded as safe. Either administration to the mother should be repeated, or, still safer, the mother during labor and the infant after delivery should each receive a percutaneous dose of vitamin K.

4. McCready, R. L.; Callahan, E. T., and Grandin, D. J.: J. Obst. & Gynec. **42**:398, 1941.

SUMMARY AND CONCLUSIONS

Vitamin K is absorbed through the skin. Its rate of absorption is enhanced by decreasing the viscosity of the solvent. The percutaneous absorption thus improved, vitamin K can be administered in concentrations low enough to avoid cutaneous irritations caused by the naphthoquinones. Suitable solvents must be used to guarantee further the stability of menadione (2-methyl-1, 4-naphthoquinone), which is highly sensitive to oxidation. Hydrocarbons meet the requirements.

From 0.01 to 1 per cent solutions of menadione in 80 parts of thin light liquid petrolatum and 20 parts of odorless kerosene are stable, noninflammable, readily absorbed through the skin, and nonirritant when percutaneously administered.[5]

Doses of 1 mg. and of 0.1 mg. of menadione percutaneously administered to infants during the first day of life were equally effective in preventing physiologic prothrombinopenia of the newborn. Doses of 0.01 mg. were effective in some infants and ineffective in others. The same amount of vitamin K in sesame oil given orally to the infants proved fully effective. This seems to indicate that quantitatively more vitamin K is absorbed through the intestinal wall than through the skin. However, the conventional dose of 1 mg. is a luxury dose, far exceeding the minimum requirement, no matter how administered.

The speed of percutaneous absorption seems not to be inferior to that of intestinal absorption and is probably superior to the speed of absorption of intramuscularly injected oily solutions of synthetic vitamin K. In 1 newborn infant with clinical hemorrhagic disease of the newborn and a prothrombin time of more than four minutes, the bleeding ceased after four hours and the prothrombin time became normal six hours after the percutaneous administration of 1 mg. of menadione.

Prothrombinopenia was completely prevented in infants whose mothers received 1 or 2 mg. of menadione percutaneously two to fifteen hours before delivery. Intervals of more than fifteen and less than two hours between administration and delivery are hazardous for the protection of the infant from prothrombinopenia. However, an effective percutaneous absorption may take place in some mothers in less than one hour.

Though the administration of vitamin K to mothers during labor is generally advocated and certainly justified, it should not be relied on for complete protection of the infant. Since the hour of delivery cannot be predicted and the interval between administration and delivery may be too long or too short, a factor of uncertainty always remains,

5. Such solutions were made available for investigational use by E. R. Squibb & Sons, New York.

whatever method of administration of vitamin K is used. Therefore, every infant should receive vitamin K immediately after birth, whether the mother received vitamin K or not.

The percutaneous administration of vitamin K to the newborn infant is a safe, simple and reliable procedure which can be carried out by the nurse as well as by the physician. One milligram of vitamin K should be applied in 0.1 cc. (4 drops) of the liquid petrolatum–kerosene solvent. Since this dose represents about one hundred times the minimum requirement, it will be effective even when carelessly applied to the infant's skin.

The general acceptance of a preventive measure frequently depends on the simplicity of its application. Hemorrhagic disease of the newborn is relatively rare; an intramuscular injection to every infant after birth seems to be an inadequate and a too drastic step in dealing with such a remote risk. The simplicity of the percutaneous administration of vitamin K may well render this valuable preventive measure acceptable as a routine procedure. It could be carried out simultaneously with the prophylactic instillation of silver nitrate solution into the eyes soon after delivery.

Dr. E. J. Davin, director of obstetrics, gave us permission to carry out this study, and Miss F. Woll gave technical help.

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THE HEART IN CHILDREN WITH THYROID DEFICIENCY

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AND
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In 1936 we reported a case of hypothyroidism [1] in a child in which one of the outstanding features was that of cardiac enlargement. This enlargement was reduced with thyroid therapy, but the heart returned to its original size when use of the medicament was discontinued. In that report we discussed the diagnostic features of "myxedema heart" and included a differential diagnosis of some of the less commonly appreciated causes of cardiac enlargement in childhood.

Since our report we have been unable to find recorded in the literature further cases of this condition in children. The latest edition of the textbook of Holt and McIntosh,[2] in a discussion of myxedema heart, contains this statement: "With this obscure condition we have had no experience." In neither Griffith and Mitchell's [3] textbook nor in Brennemann's [4] "Practice of Pediatrics" is there mention of electrocardiographic or other cardiac findings in their discussions of cretinism, while Means's [5] monograph on the thyroid gland mentions no case of cardiac enlargement in a patient younger than 16 years of age. These observations on the rarity of this condition prompt our report on 3 additional cases encountered in a series of some 60 cases of hypothyroidism in childhood. In addition we record subsequent observations on our original case.

From the Department of Pediatrics (Endocrine Clinic), University of Illinois College of Medicine and the Research and Educational Hospital.

1. Bronstein, I. P., and Baratz, J. J.: Enlargement of the Heart with Hirsuties (Myxedema Heart), Am. J. Dis. Child. **52**:128 (July) 1936.

2. Holt, L. E., Jr., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York, D. Appleton-Century Company, Inc., 1940, p. 602.

3. Griffith, J. P. C., and Mitchell, A. G.: Textbook of Pediatrics, ed. 3, Philadelphia, W. B. Saunders Company, 1941, p. 903.

4. Kennedy, R. L. J.: The Thyroid Gland, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1934, vol. 1, chap. 38, pp. 29 and 34.

5. Means, J. H.: The Heart in Myxedema, in The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937, p. 243.

FURTHER NOTES ON OUR ORIGINAL CASE

Fern S. has done well physically (sexually) and mentally with 2 grains (0.13 Gm.) of thyroid daily. Observations of the changes in the size of her heart are noted in table 2 of our original article. Since then we have recorded yearly roentgenologic measurements of the heart as follows:

Date	Diameter of the Chest, Cm.	Right Border, Cm.	Left Border, Cm.	Transverse Diameter, Cm.	Relation of Transverse Diameter of Heart to That of Chest (Cardiothoracic Ratio, %)[6]
5/24/35	20.0	3.1	8.0	11.1	50.5
5/22/36	20.4	3.1	8.4	11.5	50.6
5/18/37	20.9	3.8	8.2	12.0	50.7
5/24/38	21.2	3.9	7.9	11.8	50.5
10/ 3/39	22.5	3.9	8.6	12.5	50.5

These figures reveal that the size of the heart has remained essentially within normal limits throughout this time. The electrocardiographic recordings during this period have remained about as indicated in figure 1 *B* of our first paper. To recapitulate, the outstanding features following thyroid therapy are: (1) a reduction of the PR interval; (2) a higher voltage; (3) a higher P wave in lead III, and (4) an upright T wave in leads I and II.

Incidentally, her hirsuties, which is still, as it was originally, one of her prime complaints, has been unaffected. We believe now, as we did then, that it is probably atavistic in character. Nevertheless, because of the supposed relationship of the adrenal glands to excessive growth of hair, we investigated these glands by intravenous urography, abdominal examination and assay for the 17-keto steroids. None of these studies revealed anything significant.

REPORTS OF ADDITIONAL CASES

CASE 1.—Charlotte D. was referred to us at the age of 2 years 9 months because of "failure to grow." She was obviously a classic cretin. Before treatment her cardiothoracic ratio was 61 per cent. After treatment this was reduced to 54 per cent. Her electrocardiographic tracings are consistent with a diagnosis of myxedema heart.

CASE 2.—Mary H. came to us at 12 years of age because of "failure to develop." She was a typical cretin. We were unable to obtain any electrocardiograms for her. Her cardiothoracic ratio on admission was 67 per cent, while after six months of specific therapy it was reduced to 53 per cent.

CASE 3.—Frank D., a 22 year old obvious cretin with the development of a 7 to 9 year old child, has a 13 year old brother with hypothyroidism. This is one of the rare instances of familial sporadic cretinism. His electrocardiographic tracings are characteristic of "myxedema heart." Unfortunately, the original roentgenogram of his chest, which demonstrated a huge heart, has been lost, but after four months of active therapy his cardiothoracic ratio was still 60 per cent.

COMMENT

We have reported the results of cardiac examinations of 3 additional cretins and of continued observations of our first patient with "myxedema heart." In none of the subjects was the cardiac enlargement

6. Danzer, C. S.: The Cardio Thoracic Ratio: An Index of Cardiac Enlargement, Am. J. M. Sc. **157**:513, 1919.

as pronounced as in our original patient, but the electrocardiographic changes were similar. We should like to stress the value both of roentgenograms of the heart taken at a distance and of electrocardiographic recordings in all cases of hypothyroidism, since even in instances in which the size of the heart appears to be normal there may be shrinkage under treatment. This was previously emphasized by Lerman, Clark and Means [7] and by Swann.[8]

The first mention of the heart in myxedema appears in a review by the Clinical Society of London in 1888,[9] but the pathogenesis of the cardiac enlargement still remains conjectural. Feldman [10] concluded that the principal lesion of the heart in myxedema is essentially an interstitial edema and that therefore the size of the heart is decreased after administration of thyroid because of the loss of this fluid. This result is parallelled by the reduction of cardiac enlargement associated with avitaminosis B after the administration of the specific vitamin. Wenckebach [11] attributed the phenomenon of beriberi to a similar loss of fluid from the tissues.

Higgins [12] stated the opinion that probably in the early stages of hypothyroidism there is an infiltration of a mucin-like substance into the muscle fibers, which can be overcome by the administration of thyroid. Austin [13] expressed the belief that the enlargement of the heart is primarily a dilatation, though infiltration of the cardiac muscle as well as pericardial effusion can account for some increase in the cardiac shadow. Lerman, Clark and Means [7] assumed that the administration of thyroid decreased the size of the heart in myxedema by eliminating the interstitial edema and by increasing the muscle tone. They mentioned also the possibility of pericardial effusion's accounting for some of the enlargement. Feldman [10] stated that anemia is always present. The presence of this anemia was stressed by Landauer,[14] who suggested that as it becomes more severe the demands on the circulation increase; hence there is a gradual enlargement of the heart.

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7. Lerman, J.; Clark, R. J., and Means, J.: The Heart in Myxedema, Ann. Int. Med. **6**:1251, 1933.

8. Swann, W. C.: The Hypothyroid Heart, West Virginia M. J. **29**:346, 1933.

9. Report of a Committee of the Clinical Society of London Nominated December 19, 1883, to Investigate the Subject of Myxoedema, Tr. Clin. Soc. London (supp.) **21**:32, 1888.

10. Feldman, L.: The Heart in Thyroid Dysfunction, Illinois M. J. **70**:58, 1936.

11. Wenckebach, K. F.: Heart and Circulation in Tropical Avitaminosis (Beri Beri), Lancet **2**:265, 1928.

12. Higgins, W. H.: The Heart in Myxedema, Am. J. M. Sc. **191**:80, 1936.

13. Austin, V. T.: Myxedema Heart, Illinois M. J. **72**:417, 1937.

14. Landauer, W.: The Nature of Disproportionate Dwarfism, Sigma Xi Quart. **28**:176, 1940.

SUMMARY

The results of cardiac examinations of 3 children with thyroid deficiency and follow-up notes on our original patient with "myxedema heart" are reported.

The pathogenesis of the cardiac enlargement is discussed.

The importance of making routine roentgenograms of the heart taken at a distance and electrocardiographic tracings for children with hypothyroidism both before the beginning and after a period of treatment is suggested.

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STUDIES ON BLOOD PHOSPHORUS

II. BLOOD PHOSPHORUS PARTITION IN TETANY AND GUANIDINE POISONING

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It is the purpose of this paper to present a series of studies on organic phosphorus partition in pathologic conditions which have in common an inorganic hyperphosphatemia (tetany, guanidine poisoning). As shown in a previous communication,[1] the Lohmann and Nissen method for determining the partition of organic phosphorus compounds in the blood proved useful for the study of the relationship between intracellular and extracellular phosphorus. This method was employed in the present work.

TETANY

A case of chronic tetany in a child of 9 years offered an opportunity to analyze the phosphorus fractions in the blood during the tetanic inorganic hyperphosphatemia.

John P., 9 years old, was admitted to the hospital on March 22, 1940. The family history was irrelevant. The child had been in good health up to two years previously, when he had moderately severe mumps. During the course of this illness he had a convulsive seizure, characterized by rigidity of the whole body and twitching of the mouth. This lasted about five minutes, after which the child fell asleep. There was no incontinence or biting of the tongue. About five weeks later the child had measles and had a similar convulsive seizure. Six months later he had an attack of glandular fever with fever for one week and generalized adenopathy for several weeks. Since that time he had had convulsive seizures similar to the first about once every four months. These were preceded by no aura and showed no relation to food, to time of day or to any other possible contributing factor. There was no fever associated with these attacks. He had had two attacks in the ten days preceding his admission to the hospital. The parents thought that he had become more irritable and quarrelsome in the previous six months. During this period he had lost his appetite and about 10 pounds (4.5 Kg.) in weight. He had also complained of double vision and of seeing clouds in front of his eyes. Glasses had failed to improve this condition.

He was a well developed and well nourished 9 year old boy, who was not in acute distress but was restless during the examination and had slight twitching of his hands. The pharynx, nose and ears were normal, the tonsils moderately enlarged and the teeth in good condition. The lungs, heart and abdomen were normal. The knee jerks and biceps and triceps reflexes were equal and active.

From the Pediatric Laboratory and the Department of Pediatrics, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Behrendt, H.: Studies on Blood Phosphorus: I. Intracellular and Extracellular Blood Phosphorus, Am. J. Dis. Child. **64**:55 (July) 1942.

Ankle jerks were not elicited. There was no Babinsky and no Kernig sign. The Chvostek sign was plus-plus; the Trousseau sign, plus. The pupils were equal and reacted to light. Extraocular movements were normal. The fundus of the left eye showed diffuse deposits of black pigment throughout; a few spots could be seen in the right fundus. The disk was clear.

Two days after his admission to the hospital the child had a severe convulsion. Two days later chemical examination of the blood revealed a low calcium and a high phosphorus content. After treatment with calcium the calcium content of the blood rose and the phosphorus content fell, although the latter increased again before his discharge from the hospital.

The condition was diagnosed as hypoparathyroidism.

Treatment consisted of administration of calcium compounds intravenously and orally and of vitamin D.

TABLE 1.—*Blood Phosphorus Fractions in Tetany in a 9 Year Old Child*

	Plasma	Whole Blood							
			Phosphorus (Mg. per 100 Cc.) from						
Date	Inorganic Phosphorus, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Pyrophosphate	Hexose Phosphates	Glycerophosphate	Ester Phosphorus, Mg. per 100 Cc.	Acid-Soluble Phosphorus, Mg. per 100 Cc.	Lipid Phosphorus, Mg. per 100 Cc.	Total Phosphorus, Mg. per 100 Cc.
3/26/40	9.3	7.4	1.8	5.0	10.5	17.3	24.7	....	....
4/ 2/40	...	6.5	1.6	4.8	14.7	21.1	27.6	24.6	52.2
4/10/40	8.3	7.3	3.1	... 13.1*	....	16.2	23.5	....	....
Average in tetany	8.8	6.7	2.2	4.9	12.6	18.2	25.3	24.6	52.2
Average normal	3.9	4.0	3.9	5.5	10.9	20.3	24.3	28.1	52.4

* This figure represents the sum of phosphorus from hexose phosphates and glycerophosphate.

Chemical examination of the blood showed the following values:

Dates	Serum Calcium, Mg. per 100 Cc.	Serum Inorganic Phosphorus, Mg. per 100 Cc.	Serum Phosphatase, Units per 100 Cc. (King Armstrong)
From 3/26	6.2	9.3	...
	6.0	5.7	4.2
Through 4/4	8.3	8.0	3.3

The child's blood was analyzed on three occasions (table 1). The blood was taken not less than twenty-four hours after a convulsion, in order that possible effects of the muscular cramps (acidosis) on the phosphorus distribution might be excluded. The phosphorus fractions were determined by fractional hydrolysis according to the method of Nissen.[2] Table 1 gives the results, and chart 1 shows the respective graphs compared with graphs of values obtained under normal conditions.

The inorganic phosphorus content was high in all three samples of blood. The organic ester fractions, however, were not increased but were a little lower than average normal values for a child of this age. The acid-soluble phosphorus content was normal or slightly above. Both the lipid and the total phosphorus were within the normal limits.

2. Nissen, H.: Die Verteilung der Phosphorverbindungen im Blut von Mensch und Tier, Ztschr. f. Kinderh. **57**:289, 1936.

To summarize, no increase of the organic ester phosphorus in the blood of a tetanic child was found, although the inorganic phosphorus was greatly increased.

GUANIDINE POISONING

Most investigators agree that changes in the amount of calcium and of inorganic phosphorus in the course of guanidine poisoning are similar to those seen in tetany. In view of the scarcity of tetanic conditions among hospital and clinic patients, it was decided to test the blood phosphorus partition in rabbits poisoned with guanidine.

RABBIT 1.—A male rabbit weighing 4 pounds (1.8 Kg.) was kept for one week in the animal room before being poisoned. Its food consisted of the normal diet of the laboratory rabbits. Blood was withdrawn from an ear vein on Feb. 5, 1940. On February 6, 8, 11 and 12, 3 cc. of 10 per cent guanidine carbonate solution was given subcutaneously. Increasing signs of poisoning became apparent during this

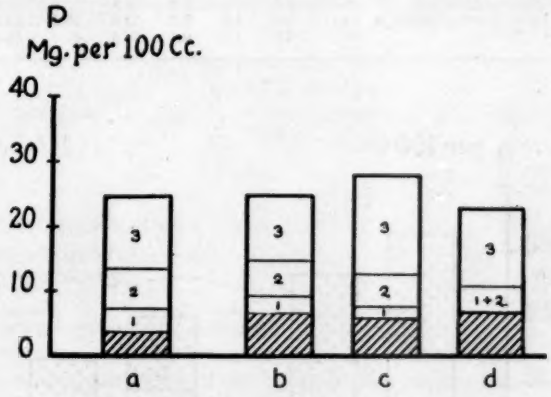

Chart 1.—Acid-soluble phosphorus fractions of whole blood in tetany of child P., 9 years of age. *a* shows the normal average for a 9 year old child; *b, c* and *d,* values during tetany. Hachure shows inorganic phosphorus; white, ester phosphorus (*1,* from pyrophosphate; *2,* from hexose phosphates; *3,* from glycerophosphate). (Oxalated blood.)

period: stiffness of the muscles, ataxia and slight muscular twitching. On February 13, at 10:45 a. m., another blood sample (5 cc.) was taken. At 11:00 a. m. 3 cc. of 10 per cent guanidine carbonate solution was injected subcutaneously. At 11:11 a. m. the animal showed signs of severe intoxication: spasms, cramps and inability to move around. Death occurred during the night.

RABBIT 2.—Another male rabbit weighing 4 pounds (1.8 Kg.) was kept for five days in the cage prior to the experiments. It was fed as the first one. On March 18, 1941, blood was withdrawn from an ear vein at 10:45 a. m. At 11:00 a. m. 3 cc. of 10 per cent guanidine carbonate solution was given subcutaneously. After ten minutes the animal became restless, jumped around and showed a definitely spastic gait, but it had no convulsions. At 5:30 p. m. blood was taken (5 cc.). The animal was definitely sick, spastic and ataxic. On March 19, 1941, at 12:30 p. m., 3 cc. of 10 per cent guanidine carbonate solution was given subcutaneously. At 12:42 p. m. signs of severe toxicity became evident: spasms, cramps, inability

to walk and finally continuous spasms of the muscles all over the body. Blood was withdrawn by heart puncture at 4:30 p. m., and death caused by the puncture, occurred at 4:50 p. m. Oxalate was added to the blood.

TABLE 2.—*Blood Phosphorus Partition in Guanidine Poisoned Rabbits*

				Whole Blood								
					Phosphorus (Mg. per 100 Cc.) from							
Rabbit No.	Date	Condition	Plasma Inorganic Phosphorus, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Pyrophosphate	Hexose Phosphates	Glycerophosphate	Ester Phosphorus, Mg. per 100 Cc.	Acid-Soluble Phosphorus, Mg. per 100 Cc.	Total Phosphorus, Mg. per 100 Cc.	Corpuscle Volume, Percentage
1 *a*	2/ 5/41	Normal.....	5.8	6.2	4.2	8.1	15.2	27.5	33.7	62.3	34
b	2/12/41	Chronic guanidine tetany	10.8	10.1	2.4	4.4	11.1	17.9	28.0	56.1	37
2 *a*	3/18/41	Normal.....	5.0	6.5	3.6	7.9	20.8	32.3	38.8	50.0	34
b	3/18/41	Subacute guanidine	5.9	6.6	4.8	8.6	15.0	28.4	35.0	50.0	34
c	3/19/41	tetany	9.3	8.8	3.5	3.7	20.4	27.6	36.4	43.3	36

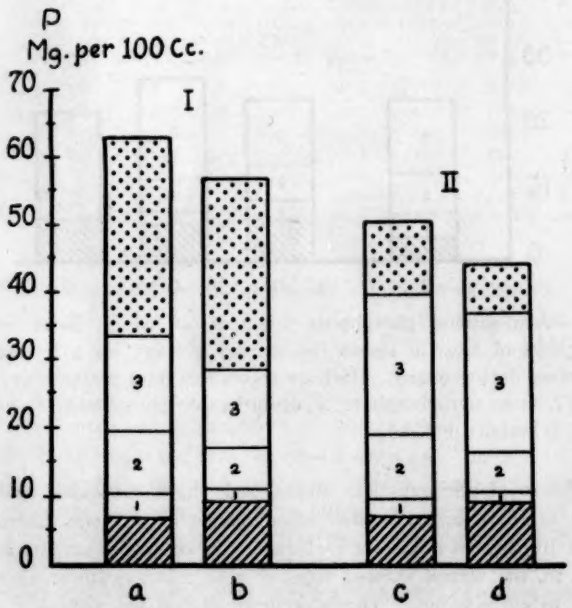

Chart 2.—Phosphorus fractions in whole blood in guanidine-poisoned rabbits (*I*, in chronic poisoning; *II*, in subacute poisoning). *a* and *c* show the normal values prior to injections; *b* and *d*, the values in tetany. Hachure shows inorganic phosphorus; white, ester phosphorus (*1*, from pyrophosphate; *2*, from hexose phosphates; *3*, from glycerophosphate); dots, lipid phosphorus. (Oxalated blood.)

The distribution of blood phosphorus in both animals is shown in table 2 and chart 2; it may be seen that inorganic hyperphosphatemia

was present in both. As compared with normal values prior to poisoning, the amounts of phsophate esters were decreased. The acid-soluble phosphorus fraction diminished in rabbit 1 and remained almost unchanged in rabbit 2. The total amount of phosphorus decreased in both animals.

The results fail to show any retention of organic phosphate esters during guanidine poisoning, notwithstanding the simultaneous rise of inorganic phosphorus in plasma and in whole blood. Is there any retention of phosphorus elsewhere but in the blood? To answer this question with regard to the muscular tissues the total phosphorus content of certain muscles of rabbits was estimated prior to and during guanidine poisoning.

Rabbits weighing 4 to 5 pounds (1.8 to 2.25 Kg.) were used. The left gracilis and sartorius muscles were cut out during anesthesia before the poisoning started. The following day, daily subcutaneous injections of guanidine compounds were

TABLE 3.—*Total Muscular Phosphorus and Calcium in Chronic Guanidine Poisoning in Rabbits*

Rabbit No.	Guanidine Compound Injected	Duration of Poisoning, Days	Total Phosphorus: Normal Animal, Gm. per 100 Gm.	Total Phosphorus: Poisoned Animal, Gm. per 100 Gm.	Total Calcium: Normal Animal, Mg. per 100 Gm.	Total Calcium: Poisoned Animal, Mg. per 100 Gm.*
1	Guanidine nitrate 0.9 Gm.; guanidine carbonate 4.2 Gm.	24	1.040	1.132	53.20	25.84
2	Guanidine carbonate 3.6 Gm.	18	1.128	1.178	61.10	29.00

* Of the dried, fat-free muscular substance.

started. The clinical condition of the animals was watched carefully, because overdosage could produce acute convulsive symptoms and sudden death. As soon as symptoms of subacute intoxication became manifest, the corresponding muscles of the right side were excised.

In experiment 1 the chronic poisoning was extended over a relatively long period (twenty-four days), from August 5 through August 29. Five and 10 per cent solutions of guanidine carbonate and 5 per cent solution of guanidine nitrate were given, each in 3 cc. doses (table 3). As soon as signs of subacute intoxication appeared, the right muscle group was removed for chemical examination. Eight hours later severe acute poisoning was manifest, and the animal died shortly thereafter.

In experiment 2 the duration of the chronic poisoning was shorter. Ten per cent guanidine carbonate solution was injected daily. During the eighteenth day of poisoning symptoms of subacute damage became manifest, and the muscles of the right side were excised (table 3). Twenty-four hours later the rabbit died.

The muscles were analyzed for their content of total calcium and total phosphorus according to methods already described.[3] The muscles were cut into small

3. Behrendt, H.: Ueber die Beziehungen der Electrolytverteilung zum Functionszustand der quergestreiften Muskulatur, mit besonderer Berücksichtigung der Tetanie, Ztschr. f. Kinderh. **41**:499, 1926.

pieces, chopped and dried at 102 C. The fat was extracted from the dried substance with ether; 0.1 of calcium and phosphorus to 1.6 Gm. of dried fat-free substance was used for a single determination. It must be emphasized that it is the dry weight of fat-free substance which has been determined. Therefore, the values in table 3 give no information about the water content, which might influence the relative phosphorus and calcium contents of the muscles.

It becomes evident from the results given in table 3 that the absolute total phosphorus content of the muscles was practically the same under normal conditions and during fully developed guanidine intoxication. Pronounced reduction of the muscular calcium, a constant metabolic feature in guanidine poisoning, was also present and gave evidence that the poisoning was highly effective. These experiments show conclusively that there is no retention of phosphorus in the muscular tissues of rabbits poisoned with guanidine.

COMMENT

Phosphorus is one of the inorganic constituents of the blood the concentration of which is changed in most clinical types of human tetany and in the various forms of experimental tetany. Much evidence has been brought forward to show that the absolute or relative increase of the inorganic phosphorus in the blood plays a decisive role in tetany, second only to that of calcium. Greenwald [4] pointed out that in tetany there is a decrease in the excretion of phosphorus, which is far greater than could be accounted for by the corresponding increase of the inorganic phosphorus of the serum. Where else could the phosphorus be retained? It seems plausible that the erythrocytes retain it in the form of the organic ester compounds. Stearns and Warweg [5] found no such increase of organic phosphate esters in rachitic tetany. Elias and Spiegel [6] and Scheer and Salomon [7] described a greater increase in the acid-soluble blood phosphorus in parathyroid and infantile tetany than the increase of inorganic phosphorus would account for. The results of the present study fail to indicate any such increase of the organic phosphorus compounds during tetany. The investigation of the blood phosphorus partition in 1 patient with nonrachitic tetany and in 2 rabbits with experimental guanidine tetany did not reveal the retention in the blood of any acid-soluble phosphorus compound except the inorganic frac-

4. Greenwald, I.: On the Phosphorus Content of the Blood of Normal and Parathyroidectomized Dogs, J. Biol. Chem. **14**:369, 1913.

5. Stearns, G., and Warweg, E.: Studies of Phosphorus of Blood: IV. Phosphorus Partition in the Blood of Children with Disease, Am. J. Dis. Child. **50**: 1164 (Nov.) 1935.

6. Elias and Spiegel: Beiträge zur Klinik und Pathologie der Tetanie, Wien. Arch. f. inn. Med. **2**:447, 1921.

7. Scheer, K., and Salomon, H.: Der Gehalt des Blutserums an säurelöslichem und lipoidem Phosphor, Jahrb. f. Kinderh. **103**:129, 1923.

tion. No conclusions should be drawn concerning the lipid fraction of the phosphorus. Close parallelism of the distribution of phosphorus in these cases of tetany and guanidine poisoning seems to confirm the general belief that the phosphorus metabolism of these two conditions is closely related. It is of interest to note that the retention of phosphorus in the blood could be confirmed in neither instance of inorganic hyperphosphatemia. It is not only true that the well established decrease in the excretion of phosphorus and the increase in the inorganic phosphorus in the blood "are out of proportion one to the other" (Collip [8]); the present experiments show in addition that both in human and in rabbit blood this retention of inorganic phosphorus in the blood is associated with a definite organic hypophosphatemia. The preponderance of the latter is obvious from the coexisting diminution of the total blood phosphorus in my analyses.

There is a second fact which does not support the retention theory, namely, the existence of normal amounts of phosphorus in tetanic muscles. That has been proved for tetany of parathyroidectomized dogs (Behrendt [3]) and has been established for guanidine tetany in the present study.

SUMMARY

In a case of tetany in a 9 year old boy the concentration of organic ester phosphorus in the blood was found normal or decreased.

In experimental guanidine poisoning in 2 rabbits the organic ester phosphorus and the total phosphorus were decreased.

The muscular total phosphorus content remained unchanged in guanidine poisoning.

8. Collip, J. B.: Parathyroid Glands, Medicine **5**:9, 1926.

THE VOMITING DISEASE

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In the winter of 1941 and again in 1942 there occurred in Charleston, S. C., an epidemic of the disease described by Zahorsky [1] as "the winter vomiting disease," or hyperemesis hiemis. Since medical literature takes small notice of this condition and since Zahorsky's contention that this is a specific disease seems to be correct, it is thought worth while to describe briefly the character of the disease as observed in Charleston.

The disease is not of a serious nature in that there is apparently no mortality associated with it, but it can be very depleting and the source of much anxiety for a few days. Except Zahorsky, Brennemann [2] appears to be the only writer whose works are available who has described such a condition. He says, "There are, however, epidemics of vomiting, with or without abdominal discomfort and some diarrhea, that are practically afebrile and offer no tangible evidence of infection. The attacks last a day or two, sometimes many days. I saw recently (November) in one family two children, one nurse, and four servants all so afflicted within a period of three days. There was at the time a widespread epidemic of this nature. The etiology is wholly in the dark. The only serious aspect lies in the fact that normal appendixes are sometimes removed at such times." Zahorsky described the disease more fully [3] and stated that the onset is abrupt and that vomiting is the outstanding feature. It persists for one or two days, is accompanied by more or less prostration, dehydration and perhaps acidosis and is usually followed by a few loose stools, which are light in color, have an extremely offensive odor and show very few pus cells. Colicky pains may be present. Fever is slight, the temperature ranging from 99 to 101 F. The leukocyte count of the blood runs from 5,000 to 13,000.

The same writer described [3] an explosive epidemic in St. Louis in February 1940 and expressed the belief that noticeably increased bacterial counts in milk used by the victims had some bearing on the development of the disease.

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1. Zahorsky, J.: Hyperemesis Hiemis or the Winter Vomiting Disease, Arch. Pediat. **46**:391, 1929.

2. Brennemann, J.: Minor Nutritional and Digestive Disorders of the Artificially Fed Infant, in Practice of Pediatrics, Hagerstown, Md., W. F. Pryor Company, Inc., 1936, vol. 1, chap. 27, p. 4.

3. Zahorsky, J.: Winter Vomiting Disease, Arch. Pediat. **57**:666, 1940.

An extensive outbreak of "gastroenteritis" in Milwaukee and its vicinity occurred during several weeks in February 1938, and the causative agent was thought to be water borne.[4] The abrupt onset, vomiting, diarrhea and abdominal pain and the short duration suggest that this supposed gastroenteritis may have been the vomiting disease with which this paper deals. An unidentified gas-forming bacterium was found in every sample of water analyzed.

The epidemic in Charleston began about the middle of February 1941 and continued through March. The number of cases was very large, running probably into the thousands, though most of the attacks were of such transient nature that they were never reported to the health department. The disease occurred among patients of all ages, but the incidence was particularly impressive among the younger children of the city. The symptoms were identical with those described by Zahorsky —abrupt onset, violent and continued vomiting, prostration, dehydration and, after a day or two, diarrhea more or less persistent. The stools were characteristically light yellow or gray and had, according to numerous volunteered descriptions, a "rotten egg odor." They did not contain any gross signs of mucus, blood or pus. In some instances vomiting was the only symptom. Diarrhea was usually not of more than two days' duration. Dehydration requiring parenteral fluids for correction was very unusual. In occasional instances the temperature was as high as 104 F. (rectal), but the fever was of short duration. The range of the few white blood cell counts which were made was from 6,450 to 16,000.

The persistent vomiting and the apparent absence of bile from the stools seemed to suggest some disease in the upper portion of the intestinal tract. The numerous children who showed this picture gave no indication of infection of the respiratory tract. A few physicians spoke of a granular appearance of the pharynx, but I did not observe this condition among a large number of patients.

The circumstances of this epidemic do not support the theory that either milk or water may be the vehicle for infection. Many of the affected children were taking evaporated milk, and a number of the patients from the adjacent rural districts were also using their own wells for water supply. Milks from various sources were used by the patients, some of whom were taking nothing but precooked foods and fresh fruit juice. Ice cream had not been generally eaten by the patients who became ill nor was there any common food factor which could be suspected. There had been no changes in diets before the illnesses

4. Edwards, A. C.; Warrick, L. F., and Muegge, O. J.: Report of Investigation of an Outbreak of Gastro-Enteritis, Madison, Wisconsin State Board of Health, 1938.

began. Not all the children in an affected family became ill; adults in such families were frequently not affected.

Children as young as 5 months of age were attacked. In families with multiple cases the time between the development of symptoms was from one to three days. A few children had more than one attack of the disease during the epidemic, and some of those who were ill in 1941 had the same condition in 1942. In October 1941 there were seen a number of patients with persistent vomiting and severe abdominal cramps without diarrhea and without signs of involvement of the respiratory tract but affected probably with essentially the same disease. No deaths were reported.

Unfortunately, no systematic bacteriologic study was made of these cases. Salmonella enteritidis was cultured from the stool of 1 patient who was severely ill. From the stool of another child with persistent mild diarrhea was obtained a coliform bacillus which formed acid and gas. Specimens of the stools of 2 children who had identical symptoms in 1940 were examined then by Dr. James D. Trask, of New Haven Conn., but no virus was found in either.

Treatment of this disease was not noticeably effective except when fluids were given parenterally. Restriction of the diet to fruit juices, carbonated drinks, crushed ice and water seemed desirable. Magnesium hydroxide in small repeated doses perhaps was helpful, and enemas sometimes seemed beneficial. Attempts at administration of sulfanilamide or one of its derivatives or of a sedative usually resulted in aggravation of the vomiting.

This account adds very little to the knowledge of the vomiting disease, but it is hoped that it may attract attention to the desirability of further investigation of a condition which is disabling and troublesome, even though it makes no appearance in the mortality tables. Without definite reason it may be suspected of being caused by a virus.

SUMMARY

A widespread epidemic of a condition characterized by persistent vomiting and diarrhea not associated with infection of the respiratory tract and of unknown cause occurred among children and adults in Charleston in the winters of 1941 and 1942.

77 Rutledge Avenue.

Case Reports

CASTOR BEAN POISONING

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Little mention has been made of castor bean poisoning in the American medical literature. This bean is the brown mottled seed of the castor plant, Ricinus communis, from which castor oil is extracted. It is about one and one-half times the size of a lima bean. Although of tropical origin, the castor plant has frequently been transplanted to the temperate zones because of its ornamental foliage.

The castor bean, because of its poisonous constituent ricin, is a potent toxic agent. In human beings severe symptoms have resulted from inhaling the dust of the bean. This has been known to cause severe anaphylactoid reactions of the respiratory system in hypersensitive persons. More commonly, however, intoxication results from the inadvertent ingestion of the bean. Ricin is an extremely poisonous protein (phytalbumin) found in the seeds along with the oil. When commercially extracted, however, castor oil contains little or no ricin.

REPORT OF A CASE

The patient, D. B., a 7 year old Italian boy, was admitted to the hospital on Oct. 6, 1941. Two days before his admission, he had eaten four castor beans, which he obtained from his father, who is a worker in a castor oil factory. Two hours after ingestion of the seeds, the boy began to vomit and he continued to do so intermittently during the remainder of the day. The next day he refused all nourishment. The parents treated him with enemas and a cathartic (phenolphthalein). The boy became drowsy on the following day and later became irrational. He was admitted to the hospita' forty-eight hours after the onset of symptoms.

On admission the child was noted to be in a stupor, from which he could be aroused. His orientation was poor, and his replies to questions were often irrelevant. He lay quietly in bed with eyes half open and extremities relaxed. The skin was cool and of a dusky gray cyanotic color. The temperature was 99 F., and the pulse was rapid (rate 140) and of fair quality. The blood pressure was 118 systolic and 70 diastolic. The remainder of the physical examination did not reveal anything unusual.

During the first twenty-four hours 2,200 cc. of 5 per cent dextrose solution in physiologic solution of sodium chloride was administered intravenously. On the

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second day small amounts of water and fruit juices were given orally. By the third day in the hospital the boy was alert, well oriented and able to take a soft, high carbohydrate diet. The blood pressure on the third day was 110 systolic and 64 diastolic.

Laboratory Data.—The blood count on admission showed: red blood cells, 575,000,000, with 15 Gm. of hemoglobin, and white cells, 20,000, of which 76 per cent were polymorphonuclear forms. The urine was normal except for a trace of albumin. Chemical studies of the blood were interesting and revealed his response to treatment.

	On Admission, Mg. per 100 Cc.	Second Day, Mg. per 100 Cc.	Third Day, Mg. per 100 Cc.
Nonprotein nitrogen	100	68	40
Urea nitrogen	65	40	25
Carbon dioxide	43	53	50
Chlorides	455	512	513
Total protein	7.98 (Gm.)	6.95 (Gm.)	6.72 (Gm.)
Total base	147	147	

COMMENT

An oral dose of 0.03 Gm. of ricin may be fatal. Death has been reported after the ingestion of but one bean. However, there is apparently a wide variation in individual susceptibility, as recovery has been reported after the ingestion of thirty beans. Symptoms of ricin poisoning [1] in man include nausea, vomiting, diarrhea, cramplike pains in the abdomen and extremities, suppression of urine and clouding of the sensorium. Renal damage, as evidenced by cylindruria, albuminuria and the clinical picture of uremia,[2] has also been reported. The terminal picture may be that of coma, convulsions or vascular collapse. The mortality [3] in a series of 150 cases is reported as 6 per cent.

Ricin acts directly on the cells and tissues in a manner similar to that of bacterial toxins. Hemorrhage throughout the abdominal viscera, particularly the entire gastrointestinal tract, is a common occurrence. On microscopic examination small foci of necrotic tissue are found in the liver, spleen and adrenal glands. Glomerular destruction and tubular necrosis are seen in the kidneys.

There is no specific antidote. Treatment [4] is evacuant; emetics are advised if the patient is seen early, and cathartics should be given thereafter. Supportive treatment with the parenteral administration of fluids is advised.

340 Henry Street.

1. Möschl, H.: Wien. klin. Wchnschr. **51**:473, 1938; Ztschr. f. klin. Med. **133**:78, 1937.
2. Abdülkadir-Lüfti: Deutsche med. Wchnschr. **61**:416, 1935.
3. Ford, W. W.: Centralbl. f. Bakt. (Abt. 1) **58**:129, 1913.
4. Miller, D. H.: M. Bull. Vet. Admin. **16**:90, 1939.

ACUTE BACTERIAL ENDOCARDITIS IN INFANCY

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Because of the relatively small number of reports in the medical literature of acute bacterial endocarditis in infancy, it has been thought worth while to report the following case, especially as we have been unable to find a similar previously reported case in which chemotherapy has been employed.

It is now a commonly accepted fact that acute bacterial endocarditis in infancy is a rare disease. The only dissenting opinion seems to be that of Loffredo,[1] who believes that its rarity is due only to failure in diagnosis. Sansby and Larson [2] made a comprehensive review of the literature in 1930, and since then the occurrence of the disease has been infrequent.

Vecchi [3] reviewed 1,060 records of autopsies of children 1 to 10 years of age at the Institute of Pathology and Anatomy at Florence, Italy, and found but 12 cases of acute vegetative endocarditis. We do not know what percentage of the patients were children in the upper segment of this age group, but admittedly it is more common in these and in older persons.

D'Ewart [4] in the *British Medical Journal* reported an instance of acute bacterial endocarditis in an infant 13 days of age.

Davis and Weiss [5] found no instances of the disease in children below 10 years of age in 5,215 consecutive postmortem examinations at the Boston City Hospital.

A case in which acute bacterial endocarditis due to the gonococcus occurred in a 10 day old infant was reported by Brandes,[6] and 1 in which it developed in a 16 month old child was reported by Sanders.[7]

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1. Loffredo, A.: Pediatria **38**:311 (March 15) 1930.

2. Sansby, J. M., and Larson, L. M.: Acute Bacterial Endocarditis in Infancy: Review of Literature and Report of Case in Five Weeks Old Infant, Am. J. Dis. Child. **39**:1261 (June) 1930.

3. de Vecchi, B.: Endocarditic Process in Childhood, Arch. Path. **12**:49 (July) 1931.

4. D'Ewart, J.: Brit. M. J. **2**:699 (Oct. 17) 1931.

5. Davis, D., and Weiss, S.: New England J. Med. **208**:619 (March 23) 1933.

6. Brandes, W. W.: Gonococcal Endocarditis in Infant Ten Days Old with Gonorrheal Conjunctivitis, Am. J. Dis. Child. **46**:341 (Aug.) 1933.

7. Sanders, C. B.: Texas State J. Med. **29**:585 (Jan.) 1934.

As far as could be ascertained there have been no reports up to the present of the treatment of the disease in this age group with sulfanilamide.

It is of interest to note that this is the first proved case of the occurrence of the disease in infancy or childhood in the seventy-eight year history of the Rhode Island Hospital.

REPORT OF A CASE

R. A., a 24 month old boy, was admitted to the Pediatric Service of the Rhode Island Hospital on July 27, 1940 with a history of illness dating back sixteen days before admission. At that time, without any known preceding infection either in the upper respiratory tract or elsewhere, he had a shaking chill, fever and profuse sweats. A local physician at the time found generalized arthralgia and a concomitant unwillingness to move either his arms or his legs. Since the onset of his illness he had had a continuous fever, looked very ill and cried at the slightest passive movement of his extremities, although at no time did they show external evidence of disease. Because of the absence of physical signs and the high fever he was sent to the hospital.

His past history revealed nothing unusual except that he had sustained a small laceration on the forehead which had healed uneventfully, about one week prior to his illness. He was born at home after a normal antepartum period and an uneventful delivery. His birth weight was 9 pounds (4,082 Gm.). With an adequate diet, his development was satisfactory in all respects. He had never been ill before and had always been considered remarkably healthy.

Physical Examination.—The temperature was 104.8 F., the pulse rate 135 and the respiratory rate 32.

General Appearance: The child was very well developed and well nourished but looked acutely ill. He was stuporous yet semidelirious. The skin was pale but showed no eruptions, petechiae or abnormal coloration.

Head: The scalp was normal, with a small well healed scar on the left side of the forehead. The development of the head was normal, and the fontanels were closed.

Eyes: The pupil of the right eye was slightly larger than that of the left; they reacted sluggishly to light. The scleras were not jaundiced, and the conjunctivas were not injected and showed no petechiae.

Ears: There was no discharge. The left ear drum appeared to be slightly red, but there was no fulness and landmarks were readily visible. The right drum was normal in all respects.

Nose: There was no discharge or injection of the mucous membrane.

Mouth: The mucous membranes were clear. Sixteen teeth were present; the tongue was well hydrated, and the tonsils were large but innocent looking. The pharyngeal walls were normal.

Neck: A slight resistance to flexion was observed, but no definite rigidity. A few shotty cervical nodes were palpable on both sides of the neck.

Chest: The development of the chest was symmetric, and there were no deformities.

Lungs: They were resonant throughout; the breath sounds were normally vesicular. No rales or rubs were heard.

Heart: The heart was not enlarged to percussion. The pulse showed a regular sinus rhythm and was rapid. The sounds were of good quality; no murmurs or rubs were heard.

Abdomen: The abdomen was soft and flat. The tip of the spleen was felt in the left upper quadrant, but no other masses or organs were felt.

Genitalia: They were normal, and the testes were in the scrotum.

Rectum: No abnormalities were seen.

Reflexes: The deep reflexes of the upper extremities were bilaterally equal and normal. The knee jerks were both hypoactive, the left more so than the right. The ankle jerks were physiologic. Kernig and Brudzinski signs were not elicited. Plantar stimulation gave normal responses on both sides.

Extremities: The left arm was somewhat flaccid but without atrophy; the left thigh was also flaccid. The right knee was held in a flexed position; it was slightly swollen and warm but not red, and there was no evidence of fluid. It resisted motion to some small degree.

Laboratory Data.—The Wassermann and Hinton reactions were negative. The Mantoux test in a dilution of 1:1,000 elicited a negative response. Chemical examination of the blood showed: hemoglobin, 11 Gm.; red cells, 3,960,000, and white cells, 13,100, with 84 per cent polymorphonuclears, 6 per cent small lymphocytes and 6 per cent large lymphocytes. Examinations of the urine gave constantly negative results; microscopic study revealed no hematuria. The urea nitrogen content of the blood was 8 mg., the dextrose content 57 mg. and the calcium content 9.1 mg. per hundred cubic centimeters. Lumbar puncture showed an initial pressure of 185 mm., normal dynamics and clear, colorless fluid, with the least possible trace of globulin, 48 mg. of protein and 64 mg. of dextrose. The fluid contained 60 white blood cells with 85 per cent polymorphonuclears. Smear revealed no organisms, and acid-fast bacilli were not found. Lumbar puncture repeated in two days showed changes in the dextrose content, which had risen to 71 mg. per hundred cubic centimeter, and in the cell count, which was now 32 per cent polymorphonuclears and 17 per cent lymphocytes. A culture of blood taken at the time of admission, July 27, 1940, grew type A hemolytic streptococci after four days' incubation. This result was repeated on July 29, August 1 and August 3. The electrocardiogram showed a rate of 151 as the only abnormality. Conduction time and all complexes were well within normal limits. Roentgenograms of the chest revealed no abnormalities in the pulmonary fields. The heart and great vessels were not enlarged; the long bones and right knee showed no evidence of pathologic change. Films of the skull and sinuses were likewise normal for a child of this age.

Progress.—There was no pronounced change in the baby's condition throughout his entire stay in the hospital. His temperature was constantly elevated, spiking up to about 104 F. daily with a base line of 101. After two days the slight swelling of the right knee receded, but his spleen was now down to about 3 fingerbreadths below the costal margin, although apparently it was not tender. The cardiac status did not change, as far as could be made out by auscultation or palpation. Fluids and blood administered parenterally produced very little change in his condition. By the seventh day in the hospital the spleen was down to the umbilicus and four painful petechiae were found on the plantar surface of the right foot. No subsequent embolic phenomena were discovered.

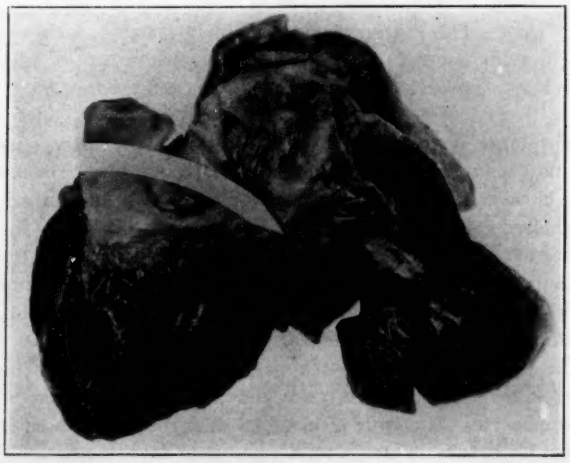
Sulfanilamide therapy was instituted on admission, and a total of 585 grains (37.85 Gm.) was given without effect on either the type A hemolytic streptococci

in the blood stream or on the clinical picture presented, although a blood level of the drug of 5.9 mg. per hundred cubic centimeters free and 8.6 mg. combined was reached on the second day and the drug subsequently continued in constant dosage.

The child died on the twelfth hospital day.

Postmortem Examination.—Postmortem examination was performed one and one-half hours after death. The body was that of a well developed and well nourished child. Petechiae were discovered on the conjunctivas, the chest wall and the feet.

When the peritoneal cavity was opened, approximately 400 cc. of brown serous fluid was found. The peritoneum itself was normal except in the flanks and in the region of the spleen, where the vessels were more apparent than usual. There were numerous filmy fibrinous adhesions between the spleen and the abdominal wall. The lower edge of the spleen was at the level of the left crest of the ilium, and the liver extended 4½ fingerbreadths below the costal margin.



Photograph of the heart, showing the vegetative growth on the nonaortic cusp of the mitral valve.

The right and left pleural cavity each contained about 100 cc. of straw-colored fluid.

The pericardium was normal, but the sac contained 60 to 70 cc. of clear straw-colored fluid.

The heart weighed 65 Gm. The chambers were of average size for a child of the patient's age. Valve measurements (circumference) were: tricuspid, 6.2 cm.; pulmonic, 3.8 cm.; mitral, 6 cm., and aortic, 3.8 cm. The aortic, pulmonic and tricuspid valves were thin, smooth, delicate and discrete. The aortic leaflet of the mitral valve was thin, smooth and glistening. The nonaortic leaflet had similar characteristics with the exception of an area on its auricular surface situated along the line of closure and extending to the free margin of the valve leaflet, which was gray, with pink areas 1 mm. in diameter. This area was 4 mm. in thickness and extended 4 mm. back from the free margin and 9 mm. along its edge. This mass was composed of friable mottled gray granular material that was loosely adherent to the leaflet. The muscle

tissue was paler than average in some areas, being a diffuse, ill defined gray-pink in the posterior part of the interventricular septum. Microscopically the cardiac muscle showed focal collections of lymphocytes and polymorphonuclear cells, eosinophils and neutrophils.

Lungs: Both lungs showed gross and microscopic evidence of bronchopneumonia.

Spleen: The spleen weighed 210 Gm. Its surface was dull and slightly shaggy from fibrinous adhesions. Gross and microscopic examination revealed an infarct on the anterior surface. The general texture of the spleen was softer than average, and microscopically it was engorged and heavily infiltrated with polymorphonuclear leukocytes and red blood cells.

Gastrointestinal Tract: There were numerous petechial hemorrhages in the submucosa of the small and large bowels. One had a yellow-white pinpoint center.

Liver: The liver weighed 660 Gm. and on section appeared to be somewhat swollen. The gallbladder was not remarkable.

Kidneys: The left kidney showed two circular gray areas 5 to 8 mm. in diameter, which were surrounded by 1 mm. of erythema and had yellow pinpoint centers. From these areas the capsule could not be stripped. Microscopic examination confirmed the impression of septic emboli. These areas extended to a depth of 3 mm. The right kidney showed similar pathologic changes.

Adrenals, Thymus and Bone Marrow: These all appeared normal, both grossly and by microscopic examination.

Bladder: One submucous petechia was seen in the bladder.

Brain: The brain weighed 1,285 Gm. The vessels of the pia-arachnoid were prominently engorged. In the region of the left motor area, 3 cc. from the midline, there was an accumulation of a gray-white thick fluid in the pia-arachnoid. On section, in the region near the calcarine fissure in the left occipital lobe there was an infarcted area 8 mm. in diameter involving gray and white matter.

Cultures of the growth on the mitral valve grew hemolytic streptococci and gram-negative rods of the colon group, and those of the blood grew hemolytic streptococci.

SUMMARY

This is a report of the case of a 24 month old white boy who was ill for sixteen days before admission to the hospital with chills, fever, profuse sweats and painful nonswollen joints. Physical examination on admission showed an acutely ill child whose positive symptoms were a palpable spleen, a somewhat flaccid left arm and a right knee held in flexion and slightly swollen. While he was in the hospital, the spleen became larger and peripheral embolic phenomena were discovered. Blood cultures taken at the time of admission and subsequently repeatedly grew type A hemolytic streptococci. Sulfanilamide, fluids and blood were without demonstrable effect. Autopsy revealed a vegetation on the nonaortic cusp of the mitral valve, which grew hemolytic streptococci of type A. The myocardium was a mottled gray, and the lungs showed evidence of congestion and bronchopneumonia. There were small infarcts of the spleen, kidney, gastrointestinal tract, bladder, skin and brain.

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AMAUROTIC FAMILIAL IDIOCY IN IDENTICAL TWINS

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Since the original descriptions by Tay in 1881 and Sachs in 1887 of amaurotic familial idiocy in infants, a great deal of knowledge has been added to the subject, and it is now recognized that this condition exists not only in the form of (*a*) infantile amaurotic familial idiocy as originally described but in three additional forms, namely (*b*) the late infantile type, (*c*) the juvenile type and (*d*) the adult type.[1] As the cases reported in this paper are instances of the classic form of amaurotic familial idiocy, to which the name Tay-Sachs disease has been given, a brief description of the disease will be limited to this form only and the others will be omitted as being beyond the scope of this presentation. Tay-Sachs disease is uncommon, though not rare; and while cases have been reported for the past fifty years, a search of the literature available to us fails to disclose any report of the infantile form of amaurotic familial idiocy in twins, either dissimilar or identical, included in the medical literature.

Though no satisfactory reason has been discovered, amaurotic family idiocy is preeminently a disease of the Jewish race, and even though it occurs in other groups and nationalities, Jewish infants are its chief victims. The heredofamilial character of the infantile type is an outstanding feature, and evidence is sufficient to indicate the disease is genetically determined and behaves as a result of an inherited recessive monomeric mendelian character.[2] Parents are normal, as would be expected with a rare recessive mendelian trait with regard to which the great majority of parents are heterozygous,[3] but the disease would be transmitted to the sibling if the faulty genes were received from both parents. Consanguinity is thus the most frequent cause of amaurotic familial idiocy, because the recessive genes are received from both parents.

From the Endocrine Clinic, Lebanon Hospital.

1. Rothstein, J. L., and Welt, S.: Infantile Amaurotic Family Idiocy, Am. J. Dis. Child. **62**:801 (Oct.) 1941.

2. Wilson, S. A. K.: Amaurotic Family Idiocy, in Neurology, edited by A. N. Bruce, Baltimore, William Wood & Company, 1940, vol. 2, pp. 827-874.

3. Jervis, G.: Juvenile Amaurotic Family Idiocy, Am. J. Dis. Child. **61**:327 (Feb.) 1941.

According to Hoben about 15 per cent of parents of infants with amaurotic familial idiocy are first cousins. The expected quota of victims in families in which the parents are carriers, neither manifesting the specific traits, can be calculated by the genetic theory. If two parents beget an infant in whom amaurotic familial idiocy develops, the odds are that one half of their progeny carry the gene recessively and that one quarter of the children will exhibit the disease. Predisposing causes other than inheritance are unknown.

The disease is roughly characterized by a triad of symptoms, i. e. paralysis, blindness and dementia. Of all the cardinal symptoms the most puzzling in the opinion of Sachs [4] was the unusual and rapid emaciation of the child. At the beginning the majority of the afflicted children are plump and well developed, but in the course of a year many of them are reduced to skin and bones. Roughly, the muscular involvement advances insidiously from normalcy to progressive stages of weakness, feebleness of motion, falling forward of the head, inability to sit or turn, weakened grasp, muscular wasting, spasticity, general contractures and inability to swallow.[2]

The ocular signs are interesting and are of diagnostic importance. The fundus is normal for the first few weeks or months of life but soon shows a certain sign of the disease in the shape of a grayish white circular path, conspicuously defined, at the center of which lies a cherry red spot, occupying the site of the macula. Atrophy of the optic nerve is another retinal lesion and is virtually constant as the disease advances. There are a multitude of other symptoms, for no part of the brain or autonomic nervous system is spared, and, depending on the degree and the site of pathologic change, the symptom complexes vary considerably. The infant descends the scale to a vegetative existence; it lies inert and indifferent. Beginning within the first six to nine months of life in most infantile patients, the disease goes on to its fatal end frequently before the second and nearly always before the third year is out.

REPORT OF A CASE

C. G. and R. G., identical twin girls, were admitted to the endocrinology clinic of Lebanon Hospital in May 1941, at the age of 13 months. The mother, R. G., was a 38 year old Russian Jewess and in April 1940 was delivered of these twin girls by breach extraction, after forty-eight hours of labor. One girl weighed 5 pounds (2,268 Gm.) and the other 6 pounds (2,722 Gm.). One baby, C. G., sustained a fracture of the left humerus, which healed easily. They were single ovum twins, there being but one placenta and one amniotic sac. The father was also a Russian Jew, aged 41 years. The parents had been married three years. The mother has two married sisters who have two grown children apiece. The father also has two married sisters with two normal children apiece. There is

4. Sachs, B.: Amaurotic Family Idiocy and General Lipoid Degeneration, Arch. Neurol. & Psychiat. **21**:247 (Feb.) 1929.

no history of any mental deficiency or of any similar condition to their knowledge in the families of either side for the past two generations. The mother and father are not related.

The children were admitted with the complaint that they could not sit up. The first tooth erupted at 6 months, and on a varied diet of cereals, vegetables, meats, fruit and milk, the children thrived well and weighed 26 and 31 pounds (11,793 and 14,061 Gm.) on admission. They were exceptionally long for their age, 31 and 32 inches (79 and 81 cm.) respectively, and presented the appearance of extremely healthy and well fed children. The examination revealed, however, that they could not hold their heads up for longer than a few seconds. They could not sit up but fell forward on their faces and made little or no attempt to kick their legs or reach for objects. They did not try to crawl or creep. They were extremely obese, but their muscles were limp and devoid of tone.

Appearance of the patients.

There was no bulging of the fontanels, and the circumference of the head of each child was 18 inches (46 cm.). There was no evidence of cretinism or rickets. Apparently they could still see, because they turned their heads slightly in following movements of the hands.

Examination of the skull of each child with reference to the sella turcica showed it to be normal in size and shape. Roentgenograms of both wrists and both lower extremities showed three carpal centers of ossification, which would be normal for the patients. However, the centers of ossification of the heads of the metacarpal bones, which were all present, seemed to have appeared prematurely. No other abnormalities were seen. Neurologic examination revealed nothing abnormal except hyperacusis. Ophthalmologic examination showed that the disk in each eye was pale but well defined, with the exception that one disk was already showing blurring on the margins. In the macular region of each eye there was a circular white opaque elevated area fading peripherally into the surrounding fundus. In the center of this area was seen the cherry red spot. The blood vessels were normal in caliber.

The spleen and liver were not palpable, and there was no enlargement of the cervical, axillary or inguinal glands. Blood counts disclosed hemoglobin readings of 80 and 84 per cent; red cell counts were of 4,900,000 and 4,720,000 and white cell counts of 7,400 each, with polymorphonuclears, 33 and 35 per cent, lymphocytes 58 and 65 and eosinophils 2 and 5 per cent. There is a remarkable similarity in the blood counts. Chemical examination of the blood revealed nonprotein nitrogen 35 mg. and sugar 100 mg. per hundred cubic centimeters in each case. The total cholesterol contents were 100 and 130 mg. per hundred cubic centimeters, and the values for cholesterol esters, 74 and 77 mg. Wassermann reactions of both the children and the parents were negative.

Since their first observance the children have shown a slow but continuous deterioration. The mother reports that they are not eating as well and do not chew as vigorously as heretofore. They seem to show no interest in food and must be forced to eat. They lie listlessly and hardly move at all. Their lusty cry has deteriorated into a hardly audible whine, and each has lost between 8 and 10 pounds (3,629 and 4,536 Gm.) in weight since they were first observed. Hyperacusis has become more pronounced, and even a mild sound will cause tonic spasms involving the hands, face, feet and neck. These attacks last from a few minutes to one hour and may recur many times a day; often they are accompanied by vomiting. Although these children still present at first glance a picture of a fairly healthy state and might easily deceive a casual observer, the telltale signs and symptoms of this hopeless condition appear on closer scrutiny.

COMMENT

The outlook for these victims of amaurotic familial idiocy is bad, since few survive the age of 2½ years and hardly any 3 years.[2] Various treatments have been tried including the use of endocrine substances,[4] but none has been of any avail. There is no means at hand for staying the progress of the disease once it becomes evident, whatever its clinical form.

It is generally agreed now that the primary lesion of amaurotic familial idiocy is in the ganglion cells [5] and is caused by faulty lipid metabolism in those cells. The disturbance, therefore, is in the nutritive rather than in the conductive mechanism of the cell. This is the striking difference from other diseases of the nervous system. The pathogenesis of amaurotic familial idiocy is still not generally agreed on, with two rival theories offered to explain this condition. The first theory presupposes that the deposits in the ganglion cell are composed of prelipids, i. e. lecithinoid materials. Schaffer and his followers [6] who have corroborated his work contend that as a result of some unexplained faulty lipid metabolism within the ganglion cell these lecithin-like products are produced. They are the direct result of neural degeneration and there-

5. Richter, R., and Parmelee, A. H.: Late Infantile Amaurotic Idiocy with Marked Cerebral Atrophy, Am. J. Dis. Child. **50**:111 (July) 1935.

6. Baker, A. B., and Platou, E. S.: Cerebral Changes in Amaurotic Family Idiocy, Arch. Path. **25**:75 (Jan.) 1938.

fore ectodermal in origin. The lesions are confined to the nervous system only and are not found in the visceral organs.[7]

Opposed to this are Bielschowsky and others,[8] who view Tay-Sachs disease as a manifestation of a generalized disturbance in the lipid metabolism throughout the entire body. They assert that as the result of the overloading of the blood and tissues by these faulty lipids a widespread invasion of the reticuloendothelial system is produced, whereby lipids accumulate in the spleen, liver, pancreas, thymus, adrenal medulla, endothelial cells of blood vessels and other organs and ganglion cells of the nervous system. They appear to be the outcome of mesodermal involvement. This theory lays stress on the discovery of characteristic gangliocellular lesions in some cases of lipoid histiocytosis—the generic name of several allied syndromes, e. g., Gaucher's disease, characterized by deposits of the complex lipid kerasin; Niemann-Pick disease, characterized by deposits of phosphatides, and Schüller-Christian disease, characterized by deposits of cholesterol.

A broad view of the subject [2] leads to the conclusion that amaurotic familial idiocy, or Tay-Sachs disease, is due to a derangement of fat metabolism dependent on some inherent biochemical error of the life of the nerve cell whereby the lecithin substances existing in the form of lipoproteins are freed from the combination, gather in increasing amount and after an interval of months and years lead to death of the cells. Pathogenesis can be summed up broadly as an inherited failure to assimilate and synthesize food in the nerve cells, the fault lying in the ganglion cells according to ectodermal theory and being due to saturation of the nervous system lipids according to the mesodermal theory. Either process results in neurocellular breakdown.

SUMMARY AND CONCLUSIONS

A case of infantile amaurotic familial idiocy in identical female twins is reported. A search of the literature available fails to reveal any similar case reported previously.

The diagnosis of infantile amaurotic familial idiocy should not be difficult if the cardinal features are kept in mind: age, racial predisposition, symptomatic triad of paralysis, blindness and mental decay, and typical lesions of the fundus. However, as noted in these cases, these signs and symptoms begin insidiously and are not fully developed for months. One must look carefully for these mild changes from the normal so that a clue may be obtained as to the true nature of the disease.

20 West Eighty-Fourth Street.

105 West One Hundred and Sixty-Eighth Street.

7. Jervis, G. A.: Amaurotic Family Idiocy, Am. J. Dis. Child. **60**:88 (July) 1940.

8. Bielschowsky, M., cited by Davison, C., and Jacobson, S. A.: Generalized Lipoidosis in a Case of Amaurotic Family Idiocy, Am. J. Dis. Child. **52**:345 (Aug.) 1936.

Progress in Pediatrics

CHILDREN IN WAR TIME

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In approaching a consideration of this subject, pediatricians should take a broad view of their interest in children. They are concerned with all aspects of the child's life—with the child as an individual. In some parts of his life their contribution to his well-being is direct and controlling; in other parts, indirect and advisory. From no part of his protection and training are they entirely excluded. The present plans for child health in this country have been perfected over a long period of careful planning. There has been a slow development in which many persons and agencies have been involved and to which pediatricians, especially the members of this society, have contributed leadership and many hours of thought and work. Progress has been made in the application of this program in all parts of the country, but in no community as yet has a perfect record of accomplishment been attained, and in many places there is great inadequacy. The war has already exerted a profound influence on the operation of this program of child health and will exert an even greater influence as the country enters more fully into the prosecution of hostilities. Many of the old problems relating to children, with which workers in the field of child health have struggled through the years, will be exaggerated, and new problems will be presented. The situation is one of great magnitude and of serious implications. To find the satisfactory solutions which will safeguard the health of children will require keen judgment and hard work from all those concerned.

There are at least four important aspects of the war which directly affect children: (1) danger zones; (2) acceleration of industry; (3) expansion of the armed forces; (4) war itself. I should like to point out briefly how each of these is operative and to indicate in outline some of the measures which need to be adopted to reduce, if not eliminate, their unfavorable effects on children.

DANGER ZONES

Danger zones are primarily along the seaboards and near probable objectives of hostile attack or sabotage.

Read before the American Pediatric Society, Skytop, Pa., April 30.

Risk of Physical Injury.—Infants and young children unable to take care of themselves during an air raid or conflagration, particularly in crowded urban communities, are especially exposed to the risk of physical injury. Interruption of the water supply and of sewage disposal would expose the population to typhoid and other diseases of the gastrointestinal tract.

Evacuation and Resettlement.—Children will be in the first priority groups if it proves necessary or advisable to move any portion of the population away from danger zones into places of greater safety. This might be in an emergency after an actual hostile incident or on a planned basis in anticipation of possible enemy activity. Children will be subject to the hazards of mass movement and congested grouping; to injury and exposure to infection; to the psychic trauma of anticipated disaster; to separation from parents or loss of parents, even to seeing them killed; to location in new environments, often without parents, and to adjustments to strange places and methods of living. The English experience is full of illustrations of what happens to children as a result of evacuation.

ACCELERATION OF INDUSTRIAL WORK

This is actual now, not potential in the future.

Rapid Growth of Defense Areas.—There are four hundred such areas now, involving a thousand communities, and seven hundred other areas are being sought. Occupation of these areas involves mass movements of population. The difficulties are the same as in evacuation but they occur without planning, and children are the first to suffer. Many of these defense areas are in rural communities and small cities, where at present the least facilities for care are available. In some areas the population has increased 1,000 per cent. The problems presented affect all economic groups; it is not a question of being able to pay for what is needed—the desired things are nonexistent.

Housing: Families are living in trailer camps, tents, shacks and other substandard dwellings. In one area in Maine, 1,000 persons are commuting 10 to 50 miles daily. It is not difficult to visualize the hardships of the past winter. The doubling-up of families has established almost slum conditions. As a by-product, so to say, the system of care for children in foster homes is being widely disrupted—the foster parents can earn more money in housing workers than in caring for children.

Education: School facilities are inadequate. Local funds are insufficient to provide more facilities or teachers. Residence barriers often present real difficulties. Any given community may well hesitate to expend local money for the education of children coming to them from

long distances to remain only for "the duration." Children sit two in a seat, and double-shift sessions occur. In one Texas town 500 children of school age can be seen on the streets at any hour.

Health and Medical Care: The shortage of physicians in the defense areas is often acute. Not only is there an increase in population, but many physicians formerly in these communities have now gone into military service. The population of one community expanded from 500 to 10,000; there is one doctor 75 years old and no hospital. There is an acute shortage of hospitals in many areas. Often there are no pediatricians. Fifty per cent of the certified pediatricians are concentrated in five states. Of the more than 3,000 counties in the United States there are certified pediatricians in less than 10 per cent. One per cent of the counties, with 25 per cent of the population, have 55 per cent of the pediatricians.

Demand for Labor.—Men Away from Home: Though in many instances, as already cited, the family moves with the worker, in many other instances the father leaves home, with the inevitable effect on family life.

Women in Industry: Mothers are being increasingly drawn into industry, with the result that children are left unsupervised and the home, as such, no longer exists. The young children lack protection, and the older ones are thrown on the streets. This will increase. The mothers of the industrial groups expect it but are disturbed as to what will happen to their children. Often the father and mother are both working but in different shifts. One survey in Connecticut found 70 per cent of the mothers of the school group investigated employed. Of 277 families in one town in Alabama, 114 of the mothers were employed. This has created a great increase in the demand for day care for children. Now children are left indiscriminately with neighbors or locked in the house while the mother is away. In one community 236 preschool children whose mothers were employed had no facilities for care in the daytime.

There is already a shortage of teachers because of the greater income received from work in industry. This is especially true of teachers in rural communities.

The experience in Massachusetts is typical: One hundred and eleven of 162 school superintendents report that there is already evidence of a shortage of teachers; attendance at teachers' colleges has fallen off 10 per cent this year; 300 teachers retired in 1940 and 1,400 in 1941; students in the teachers' colleges are already teaching, and refresher courses are being offered for married women who taught before marriage but have not taught for several years. Statements by the United States Department of Education indicate that similar situations exist in other States.

There is a shortage of other trained personnel, especially in social agencies working with children, which under the present conditions need expansion.

Women to take charge of foster children are needed. An efficient system of foster care is hard to build up; satisfactory facilities cannot be augmented quickly. There may have to be a return to the institutional care of infants, with all its hazards. And where are the institutions?

Girls who falsify their age rush to these expanded industrial areas looking for jobs. They find them in restaurants, hot dog stands and similar places, which furnish an excellent recruiting ground for prostitutes.

Child Labor.—This may have a deleterious effect on health and result in the interruption of education. The increase in child labor in the country as a whole for 1941 over 1940 was: among children 14 and 15 years of age, 80 per cent; among children 16 and 17 years of age, 100 per cent (200 per cent in several states and 390 per cent in one state). The number of public employment agencies for the placement in labor of children under 16 years of age in the peak months rose from 2,000 in 1939 to 5,000 in 1941.

Some of this work is not harmful. It is necessary to consider the age of the child, the hours of labor, the type of employment and the wages received. In industry certain principles need to be established so that the younger groups are excluded from hazardous occupations. If the principle of equal pay for equal work could be adopted, the exploitation of children by paying low wages, which has been one of the chief incentives for child labor, would be obviated.

In agriculture there is a great opportunity for children to contribute toward the war effort, especially since there is an acute shortage of adult workers, but there are also dangers to health which must be avoided.

EXPANSION OF ARMED FORCES

Absence of the Father.—Absence of the father from home produces the consequences already noted in relation to the father who goes to an industrial area. The loss of the father is the greatest single hazard to the security of family life.

Early Marriage and Unmarried Mothers.—An increase in illegitimacy is already apparent. Many 14 and 15 year old girls are rushing into hasty marriages or are becoming pregnant without the formality of previous marriage to the fathers of their children. The results are evident in the rising birth rate, and one may safely predict there will be no reduction in the immediate future. Some of the hasty marriages will result in equally hasty divorces, and many of the children born out of wedlock will become patients of child guidance clinics.

Withdrawal of Doctors and Other Trained Medical Personnel from Civil Practice.—This is already evident in community life and in hospitals, and it will increase. In one community of 25,000 people there were five doctors; three are now in the service; the two left had retired. In one city of over 100,000 population there were six obstetricians; three are in service. All physicians have seen the effect in the hospitals where they work, in the care of patients in the wards, in teaching and in research.

WAR ITSELF

War as such, over and above its effect in the other particulars already mentioned, especially in the disruption of family life and the sense of insecurity which it engenders, produces in children an emotional reaction, more subtle and more devastating than the physical effects already discussed. In the very young, this results in fear, fostered by the conversation of grown-ups about the war, by the radio, and, in those who can read, by the newspaper accounts of cruelty and killing. These disturbances are more easily overcome in young children by an increase in facilities for child care than in older children and adolescents, who react by some form of delinquency. In England, in the first years of the war delinquency increased 20 to 40 per cent. In one area in this country it has increased 500 per cent over a year ago. The causes for this are many; among them one may mention the letdown in discipline and lowered standards in family life, the new environment in which many find themselves, the general nervous tension, the glorification of killing as an act of heroism, the unoccupied free time and the greater amount of money available because of higher wages.

COMMENT

These, in brief, are the facts about children in war time—the children of this country, today. The question we pediatricians should ask ourselves is: What are we going to do about it? I should like to indicate certain specific things which can be done and to outline some general procedures which may be adopted to meet a few of the situations with which we are confronted.

To assist in safeguarding children in the danger zones, some method of identification and registration should be adopted on a national scale. This will be of assistance in the event that children become separated from parents, and it will be a measure of assurance to parents. The form of identification tag presents some difficulties which thus far have not been solved. Metal tags are obviously desirable, but metals are on the priority list, and no satisfactory substitute has been found. It is desirable that the inscriptions on the tags should be uniform; the name and address certainly should be entered and probably also a number for referring

to other data filed elsewhere. Should the tag also indicate whether the child has been inoculated with tetanus toxoid or is diabetic? These questions have not been answered by federal authorities. Many states are waiting for further instructions.

Children should be immunized against those diseases for which there is a dependable and generally accepted procedure. May Day (Child Health Day) this year was dedicated to stimulation of the program of vaccination against smallpox and immunization against diphtheria. How successful this campaign has been must await subsequent surveys. Whooping cough is certainly an important disease from which to protect children. Inoculation with tetanus toxoid would seem to be especially indicated under war conditions. Typhoid may become prevalent again if there is interference with the water supply through enemy action.

Evacuation plans should be developed, with particular attention to the needs of children and to safeguarding the health of children in the communities to which they may be sent. Not the least important of these plans is provision for adequate health supervision and facilities for the care of the sick. To combat the fears of children, one effective method is to make them participating partners in the protective plans of the home and the community. The constructive energies of children and young people may well be utilized in many ways. They can help in blackout preparations and have definite responsibilities in an air raid. In Massachusetts, the Boy Scouts are assigned to duty as messengers in report centers—called to duty like other officers of the Civilian Defense Organization in case of emergency. They are made to feel themselves to be an integral part of the protection of the community, as in fact they are.

Day care for children in areas around defense industries must be extended. This requires money and trained personnel. Since personnel is not available, short training courses must be given. Volunteers under the supervision of trained workers will have to carry much of the routine. There should be a greater utilization of camp facilities, particularly for groups in danger zones. The movement to camps from home areas might well serve as a trial for evacuation plans.

Recreational facilities of all varieties should be greatly augmented. This is particularly true of those designed for the adolescent. The commercial groups will not hesitate to recognize their opportunities, and if this field is left uncovered the resulting development of poolrooms, cheap dance halls and the like need not be stressed to indicate the undesirable consequences. In England, at the outset of the war many of the youth agencies curtailed their programs because of lack of financial support. Juvenile delinquency increased to such an alarming extent that they have now been expanded under government subsidy. People in the United States may well learn a lesson from their experience.

Child guidance activities and the organization of clinics for this work must be expanded. Pediatricians must all become more efficient psychologists. They are in the habit of dealing with the emotional disturbances of children in their daily practice; they will need to exercise their art with greater skill and on a wider scale than ever before.

Health supervision, which has been advocated for many years as desirable for every child during the period of growth, should not be allowed to fall into disuse because of pressure from other duties. The youths of high school age particularly need guidance, not only to keep them from emotional catastrophies but in order that their physical condition may be adequate to meet the demands which lie ahead of them.

Child labor standards must be enforced where their relaxation will put in serious jeopardy the health of children, particularly if the deleterious effects may outlast the present emergency. We pediatricians should be ready to advise those in authority as to where and how far the peace time standards may be relaxed without serious harm. Constructive guidance from us will be welcome, but it must be based on an understanding of the labor problem and the adaptability of the child. We must cooperate with educational authorities in this matter, so that the children under 16 years of age may continue their school program with as little interference as possible. If children in the older age group are employed away from home, consideration must be given to the living conditions to which they will be subjected.

There will certainly be some adjustments in the organization of medical practice. There should be some redistribution of medical personnel, especially of pediatricians. Hospital facilities will have to be developed in many communities. Clinics will take the place of office and home visits. Conservation of the physician's time will become a matter not of convenience but of necessity. Subsidiary personnel will have to take over many functions now performed by the physician. Short courses will have to be conducted to train such personnel; much of the work may be on a voluntary basis. In every agency dealing with children—and this includes the pediatrician—their work and program must be studied with great care; every procedure must be reevaluated. Two questions should be asked: 1. What can be curtailed, suspended or modified? 2. What needs to be expanded to help meet the special needs of the day? Modifications of program are needed to: (1) release trained personnel for the war effort either in some other work or in some other locality; perhaps to train subsidiary personnel; (2) utilize auxiliary voluntary personnel to release those with particular training for special jobs, and (3) save money which is needed in some other activity associated with the war (community chests will need to reallocate their funds with the war needs in mind). In making these changes it should be the aim to

maintain so far as possible the standards of child health which have been developed over many years and which at the outset of the war were far from being adequate in many communities. Such modifications in procedures as will be necessary in the face of the present emergency should be made with as little disruption of the long time program as is possible and in those particulars which will be least likely to be detrimental to the health of children. The changes should be on a clearly understood temporary basis, and it must be shown that they truly will aid the war effort.

Expansions of programs will require full utilization of existing facilities, conservation of trained personnel and substitution of less well trained or partially trained persons wherever possible. Volunteers can replace paid workers in many instances. No fixed rules can be established which would be applicable all over the country. Each community has its own problems, and these must be met at the local level through local planning. It is evident, however, that no community can meet all of the responsibilities without calling on resources beyond its own borders. The state and federal authorities must contribute assistance in the form of advice, personnel and money.

66 Commonwealth Avenue.

DIAGNOSIS OF STREPTOCOCCOSIS IN CHILDREN

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Diagnostic methods begin at the bedside. There are certain clinical manifestations of infection by hemolytic streptococci which for all practical purposes settle the diagnosis. The most widely known of these are (1) scarlet fever and (2) erysipelas. Others which are almost as diagnostic are: (3) the fiery red throat, often with exudate, observed in older children; (4) visible cervical adenitis, and (5) a spontaneously discharging ear. These signs may represent infection by another microorganism, just as a scarlatinal rash may be caused on occasions by staphylococci, but the odds are strongly in favor of a streptococcic causation.

In cases of a less obvious variety of streptococcosis a history of recent occurrence of any of these manifestations in other members of the family is often helpful, especially if it is appreciated that streptococcic disease varies clinically within the family just as it does in unrelated patients. For example, in the case of a child with suspected scarlet fever a history of recent cervical adenitis or otorrhea in a sibling is almost as strongly suggestive of scarlet fever in the patient as though the sibling had had scarlet fever.

Figures 1 and 2 illustrate this point. The 2 families tabulated are typical of the 40 families which an associate and I are studying.[1]

There are 4 members in the first family: the father, the mother and 2 children, of 3 years and 1 year respectively. On November 18 Jeanne became feverish, and four days later she had a visible tender swelling in her neck. She was admitted to New Haven Hospital on November 25, at which time a cervical abscess was incised. Four days after Jeanne became sick, Joseph acquired a purulent rhinitis, which lasted for about one week. He had no real fever. Soon afterward the father and mother became ill with fever and a sore throat, and a cut on the mother's

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Read at the meeting of Region I of the American Academy of Pediatrics, New Haven, Conn., March 28, 1941.

Aided by a grant from the Fluid Research Fund of the Yale University School of Medicine.

From the Department of Pediatrics, Yale University School of Medicine, and the Children's Clinic of the New Haven Hospital.

1. Dr. Philip A. Bearg, of the New Haven Department of Health, is collaborating in this study.

wrist became infected. Hemolytic streptococci were obtained in cultures of materials swabbed from the father's and mother's throats, from the mother's infected wound and from Joseph's nose and in a culture of pus from Jeanne's infected gland. They were identified as group A,

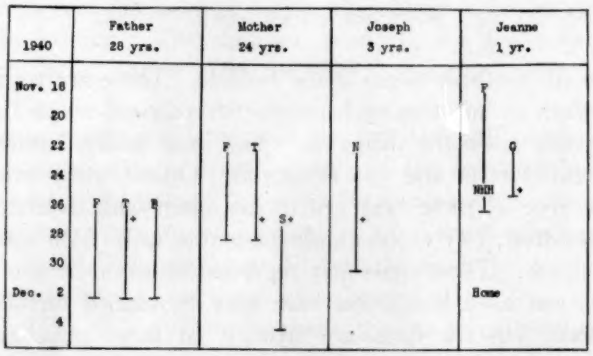

Fig. 1.—Clinical history of the L. P. family. *F* indicates fever; *T*, sore throat; *B*, that the patient was confined to bed; *G*, cervical adenitis; *N*, purulent rhinitis; *S*, cutaneous infection; +, presence of hemolytic streptococci in a lesion; *NHH*, that the patient was in the New Haven Hospital.

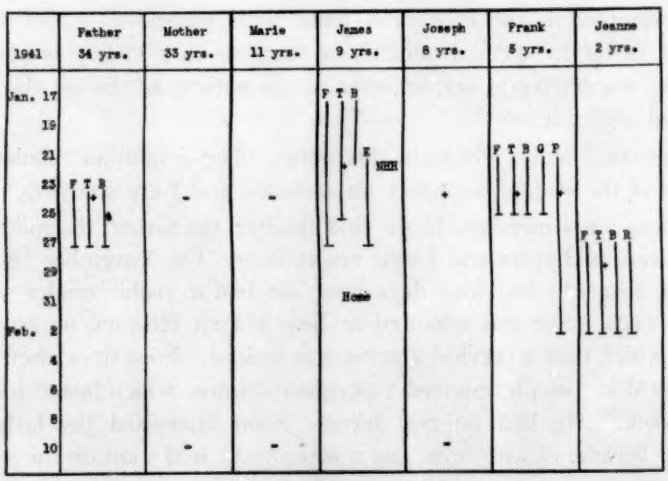

Fig. 2.—Clinical history of the F. C. family. *F* indicates fever; *T*, sore throat; *B*, that the patient was confined to bed; *R*, scarlatinal rash; *E*, erysipelas; *G*, cervical adenitis; *P*, paronychia; +, presence of hemolytic streptococci; *NHH*, that the patient was in the New Haven Hospital.

type I organisms. Two days after the first visit, one of the investigators became ill with a streptococcic sore throat, and the other acquired an infected finger with axillary adenitis. Streptococci from both lesions were group A, type I strains.

There are 7 in the second family: the father, the mother and 5 children, aged 11, 9, 8, 5 and 2 years. On January 17 James became feverish and complained of a sore throat. Four days later erysipelas developed, and he was admitted to New Haven Hospital. On the same day, January 21, Frank became ill with a sore throat, swollen cervical glands and a paronychia. Shortly afterward the father was confined to bed with a sore throat. Then Jeanne contracted scarlet fever. Hemolytic streptococci were obtained in cultures of material from the 4 sick members and from Joseph, who was a temporary carrier. The streptococci were identified as group A, type I organisms. The mother and Marie remained well, and cultures of material from their throats did not yield the organisms.

There are nine groups of hemolytic streptococci, which are differentiated by means of the Lancefield precipitin test.[2] The serologic groups are named alphabetically, and their significance is well established. Group A organisms are almost invariably the cause of human disease, and members of other groups are of little importance in pediatric practice.[3] Group A consists of about thirty types, which can be identified either by another precipitin test[4] or by slide agglutination.[5] These types are designated numerically. Studies on types of hemolytic streptococci have not progressed to the point where it can be said that they have the same significance as pneumococcic types, in which virulence is closely associated with the type and the low-numbered types are the most highly pathogenic. In our brief experience types I and III seem to be important types in New Haven—at least they have been for the past few years—as they are a common cause of disease and seem responsible for the most severe illnesses.

Cultures are valuable in corroborating the clinical diagnosis and in identifying those streptococcic infections which are less obvious. The isolation of hemolytic streptococci in a culture of blood or of material from a purulent lesion, such as suppurative otitis media, suppurative cervical adenitis or a cutaneous abscess, indicates that these organisms are the cause of the infection. Unlike organisms such as diphtheroids and staphylococci, hemolytic streptococci are rare contaminants. To my

2. Lancefield, R. C.: A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, J. Exper. Med. **57**:571 (April) 1933.

3. Boisvert, P. L.: Human Hemolytic Streptococci from Diseases of Children, Am. J. Dis. Child. **59**:281 (Feb.) 1940.

4. Lancefield, R. C.: The Antigenic Complex of Streptococcus Haemolyticus: I. Demonstration of a Type-Specific Substance in Extracts of Streptococcus Haemolyticus, J. Exper. Med. **47**:91 (Jan.) 1928.

5. Griffith, F.: The Serological Classification of Streptococcus Pyogenes, J. Hyg. **34**:542 (Dec.) 1934.

knowledge my colleagues and I have never recovered hemolytic streptococci from such sources during life without clinical evidence that they were causing disease.

From the standpoint of general usefulness, cultures of material from the throat are the most important of the cultures, because the primary lesion in the large majority of patients with streptococcic infections is in the throat and the variations in the clinical picture are the result of absorption of toxin, as in scarlet fever, or of bacterial spread, as in otitis media.

The photograph in figure 3 shows the result of a culture of material from the throat of a child with scarlet fever. The hemolytic colonies

Fig. 3.—Culture of material from the throat of a child with scarlet fever.

are hemolytic streptococci. Materials for culture are taken by swabbing both tonsillar regions and the posterior part of the pharynx with a cotton-tipped applicator. The swab is then smeared over a small crescent-shaped area at one side of the rabbit's blood agar plate and streaked out with a platinum loop. The plate is incubated overnight, or longer if indicated.

The identification of hemolytic streptococci by appearance of the colonies alone on a rabbit's blood agar plate is unreliable. The so-called Bacillus X, a common inhabitant of the throat, produces a hemolytic colony which is strikingly similar to those of hemolytic streptococci. However, the distinction can easily be made by a stained smear—the

one is a gram-positive coccus and the other a gram-negative rod. Krumwiede and Kuttner [6] advocate the use of sheep's blood, because it inhibits the growth of Bacillus X but does not affect the hemolytic streptococci.

How reliable is a culture of material from the throat in the diagnosis or exclusion of a streptococcic infection? I should like to use our data to indicate how often hemolytic streptococci may be found in the throats of children with streptococcosis and how often these organisms are recovered from the throat in the absence of recognizable streptococcic disease. Cultures of material from the nose and throat are part of the admission examination of all patients, except premature infants, who are admitted

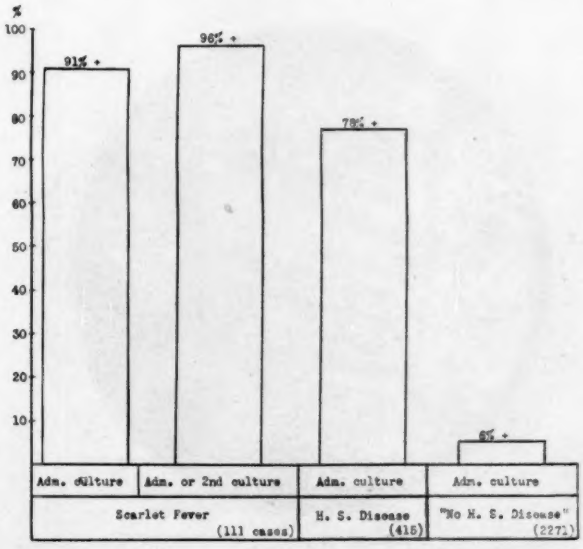

Fig. 4.—Cultures of material from the throat that yielded hemolytic streptococci.

to the wards of the children's clinic of New Haven Hospital. During the years 1938, 1939 and 1940 throat cultures were made for 2,686 patients. Four hundred and fifteen of these patients had a streptococcic infection, including 111 with scarlet fever; 2,271 had no recognizable streptococcic disease. In figure 4, patients with scarlet fever are considered separately because they were admitted early in the disease and because the data on them indicate how often hemolytic streptococci are

6. Krumwiede, E., and Kuttner, A. G.: A Growth Inhibitory Substance for the Influenza Group of Organisms in the Blood of Various Animal Species: The Use of the Blood of Various Animals as a Selective Medium for the Detection of Hemolytic Streptococci in Throat Cultures, J. Exper. Med. **67**:429 (March) 1938.

found in the throats of patients seen during the first few days of a streptococcic infection. The cultures made on admission yielded the organism in the cases of 91 per cent of these patients. When a second culture was made for those children with negative results on admission, the total incidence of positive results was 96 per cent. Throat cultures made on admission gave positive results for 78 per cent of the 415 patients with streptococcic disease. The 111 persons with scarlet fever are included in this group. This figure indicates the percentage of patients with a streptococcic infection, regardless of the stage of the illness or the site of the lesion, from whose throats streptococci were obtained on culture. This figure is lower than that for scarlet fever for two reasons:

Fig. 5.—Culture of material from the nose of a child with scarlet fever.

(1) Frequently the patients had been sick for some time, and (2) in a fair number the presenting lesion was not in the throat but was manifested in another form, such as erysipelas or an infected wound. In spite of these conditions there is still a high incidence of positive results of throat cultures.

The so-called carrier rate was 6 per cent. In other words, 169 of the 2,271 patients without recognizable streptococcic disease had the organisms in their throats.

Cultures of material from the nose have advantages which deserve consideration. Culture of such material from a well child shows only a few colonies of staphylococci and diphtheroids. This is in contrast to the normal flora of the throat, which is complicated and contains organisms which resemble hemolytic streptococci in the appearance of

the colonies. In sick children, hemolytic streptococci are frequently found in the nose. This we take to be a sign of bacterial activity. The presence of these organisms, often in large numbers, makes a striking picture.

The photograph in figure 5 shows the result of culture of material from the nose of a child with scarlet fever. Hemolytic streptococci are present in large numbers.

Materials for culture are taken by tilting the tip of the nose upward and gently inserting a cotton-tipped applicator backward along the floor of the nostril until the posterior part of the nasopharynx is felt.

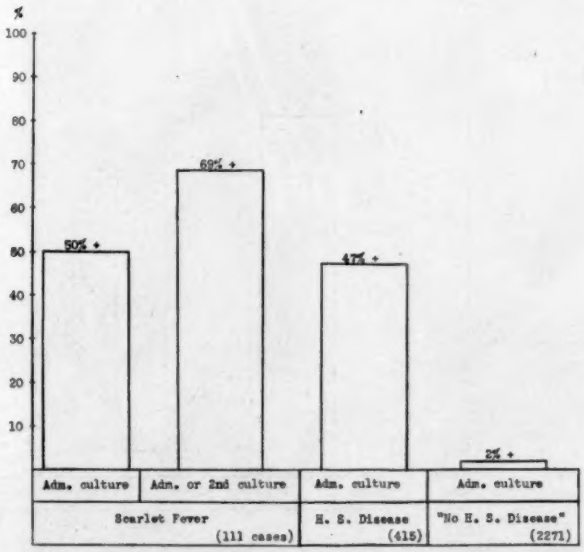

Fig. 6.—Cultures of material from the nose that yielded hemolytic streptococci.

Figure 6 is similar to figure 4 except that the material was obtained from the nose. Cultures of material from the nose made on admission yielded hemolytic streptococci in the cases of 50 per cent of the patients with scarlet fever. When a second culture was made for the patients who had negative results at first, the total percentage of positive results was 69 per cent. Nasal cultures on admission gave positive results for 47 per cent of the patients with any type of streptococcic infection. The incidence of positive results of nasal cultures for children without apparent streptococcic disease was very low, 2 per cent.

Nasal cultures are of value in complementing throat cultures. As is shown in figure 7, the use of both cultures increases the incidence of isolation of streptococci on admission of patients with scarlet fever or with streptococcic disease in general by 5 per cent over that obtained

with throat cultures alone. Nose and throat cultures made on admission revealed the organisms in 96 per cent of the patients with scarlet fever—the same percentage as that obtained with a repeated throat culture. Although nasal cultures do not give positive results as frequently as throat cultures in cases of streptococcic disease, the results are highly specific.

Experience in this laboratory and in others indicates that the importance of good mediums cannot be overemphasized. A fresh beef heart infusion with 1 per cent neopeptone is the basic medium used in this laboratory. (Neopeptone is used in the preparation of the medium because bacteriostatic substances are frequently present in ordinary

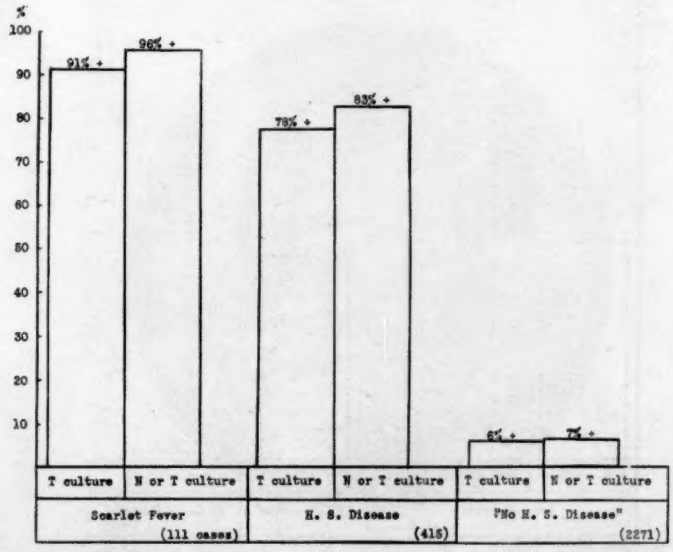

Fig. 7.—Cultures of material from the nose or throat made on admission to the hospital that yielded hemolytic streptococci compared with cultures of material from the throat alone.

peptones.) Blood agar plates containing 5 per cent rabbit blood are made daily. With the change to this medium in January 1937 an improved growth of hemolytic streptococci, as well as of other common pathogens, was immediately apparent. A review of our laboratory data corroborates this impression. During the three year period (1934 to 1936) prior to the use of fresh beef heart medium, throat cultures made on admission yielded hemolytic streptococci for 74 per cent of the patients with scarlet fever and nose cultures gave positive results for 22 per cent. This is to be compared with 91 per cent and 50 per cent respectively for the years 1938, 1939 and 1940, as reported in this paper.[7]

7. The cultures were examined by Mrs. Mildred D. Fousek, who has been bacteriologist in this laboratory since 1934.

Serologic tests furnish an additional means of diagnosis. There are two in general use: the antistreptolysin test [8] and the antifibrinolysin test.[9] The antistreptolysin test is highly specific, but we use the antifibrinolysin test because it is inexpensive and simple enough for routine clinical use. Hemolytic streptococci will rapidly dissolve the plasma clots of normal persons, and a positive reaction to the test depends on the presence in the patient's blood of a substance which makes the clot resistant to liquefaction.

Fig. 8.—Reactions to the antifibrinolysin test. The tube on the left shows a solid plasma clot; the one in the center, a lysed clot, and the one on the right, a resistant clot.

Figure 8 shows at the left the clot which forms after the patient's plasma, a stock culture of hemolytic streptococci and calcium chloride are mixed. The tube is inverted to show that the clot is solid. The middle tube contains a dissolved clot. The reaction in this case was

8. Todd, E. W.: Antigenic Streptococcal Hemolysin, J. Exper. Med. **55**:267 (Feb.) 1932.

9. Tillett, W. S., and Garner, R. L.: The Fibrinolytic Activity of Hemolytic Streptococci, J. Exper. Med. **58**:485 (Oct.) 1933.

read as negative because complete liquefaction occurred within one hour. One hour is the upper limit of normal. The clot in the tube at the right is still solid at the end of twenty-four hours. This is a 4 plus reaction. When complete liquefaction occurs in three, eight or twenty-four hours, the reaction is read as 1 plus, 2 plus or 3 plus respectively.

Figure 9 shows the clinical course of the disease and the results of an antifibrinolysin test in an 8 year old child with scarlet fever. She was admitted to the hospital on the second day of the disease with a temperature of 103.5 F. The reactions to the antifibrinolysin tests were negative early in the illness and then became increasingly positive. The positive reaction persisted for about three weeks. The test gives a positive reaction in about 80 per cent of cases of streptococcic infection in children, and at a time when in the absence of suppuration it may be difficult to recover the streptococci by cultural methods. It is rather

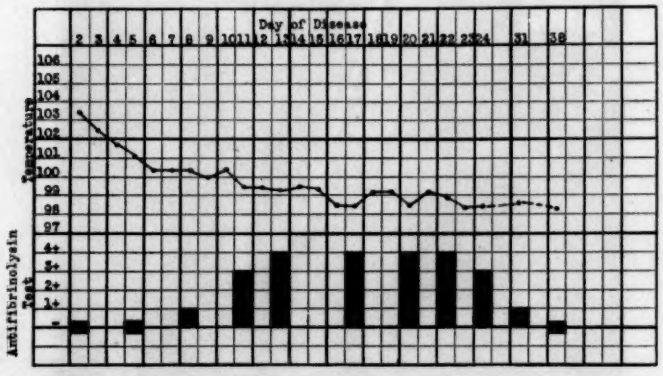

Fig. 9.—Results of antifibrinolysin tests in an 8 year old child with scarlet fever.

characteristic of streptococcosis in children that in the absence of a rash the patient is admitted to the hospital in the second or third week of the illness. It is the persistence of the illness and not a stormy onset which is frequently responsible for the child's being brought to the hospital. This holds true for dispensary as well as ward patients and is probably also true of children examined in the home.

The test is not entirely specific in pediatric practice.[10] Positive reactions may be found in such diseases as pneumococcic pneumonia. Such exceptions prevent one from making a definite diagnosis of strepto-

10. Boisvert, P. L.: The Streptococcal Antifibrinolysin Test in Clinical Use, J. Clin. Investigation **19**:65 (Jan.) 1940; Qualitative Differences Between Positive Streptococcal Antifibrinolysin Tests, Proc. Soc. Exper. Biol. & Med. **49**:678 (April) 1942.

coccic disease purely on the basis of a single positive reaction. However, a positive reaction to the test during the course of an illness or a second positive reaction a few days later makes clear the diagnosis.

SUMMARY

This study indicates that four methods are available for the diagnosis of streptococcosis in children:

1. Clinical: Infection by hemolytic streptococci can frequently be recognized by its classic manifestations—scarlet fever and erysipelas. A fiery red throat, visible cervical adenitis and a spontaneously discharging ear are signs which strongly suggest streptococcic disease, but the clinical impression should be corroborated bacteriologically if possible.

2. Bacteriologic: Cultures are important adjuncts or may in themselves settle the diagnosis. The presence of hemolytic streptococci in the nose or throat of a child is usually significant and in conjunction with clinical evidence indicates disease. The demonstration of hemolytic streptococci in material from purulent lesions is in itself diagnostic.

3. Serologic: Antifibrinolysin or antistreptolysin tests are especially useful in protracted illnesses.

4. Epidemiologic: Evidence of recent streptococcic disease in the family furnishes a valuable lead to the diagnosis in the patient. This method consists of the application of methods 1, 2 and 3, alone or in various combinations, to the other members of the family.

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STREPTOCOCCOSIS IN CHILDREN

A NOSOGRAPHIC AND STATISTICAL STUDY

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AND

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From consideration of the patients who come to the university children's clinic of the New Haven Hospital one gets the impression that the majority of them fit into one or the other of two quite dissimilar categories—children with disorders of behavior and children with acute infectious diseases. Of the acute infectious diseases there are two main groups, namely, the pneumonias and the diseases caused by infection with beta hemolytic streptococci. We do not have data regarding the proportion of streptococcic infections in private practice; but bearing in mind epidemics in schools and army cantonments, one would suppose that the crowding and the inadequate sanitary facilities characteristic of the homes of patients who make up dispensary and ward clientele would favor the acquisition and transmission of streptococci by such persons rather than by those of better economic status.

Consideration of the subject prepares one to appreciate fully the introductory paragraph to the section on "Streptococcal Infections," by Dawson[1] in Cecil's "Textbook of Medicine":

> Streptococcal infections comprise a wide and varied group of clinical conditions. It is probably not an exaggeration to state that streptococci are responsible for a greater variety of pathological processes than any other group of bacterial agents. Not only are they the direct cause of a large number of distinct diseases but, owing to their wide distribution, they are also important secondary invaders. In addition, streptococcal infections appear to initiate certain other disease processes, the precise nature of which is not clearly understood.

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† Dr. Trask died on May 24, 1942.

This study was aided by a grant from the Fluid Research Fund.

Read at the meeting of Region 1, American Academy of Pediatrics, New Haven, Conn., March 28, 1941.

From the Department of Pediatrics, Yale University School of Medicine, and the Children's Clinic, New Haven Hospital.

1. Dawson, M. H.: Streptococcal Infections, in Cecil, R. L.: A Textbook of Medicine, ed. 5, revised, Philadelphia, W. B. Saunders Company, 1941, p. 166.

And, in the words of Longcope,[2] it is probable

> . . . that the variety, the special character, the severity, and the outcome of infections by hemolytic streptococci are determined by many factors. The disease will depend on the one hand upon the predominance of one or another of the biologic properties of the infecting organism and on the other upon the varying states of resistance or susceptibility, immunity, or allergy that modify the responses to infection in the host. It is the interaction of these forces that is responsible for the variegated clinical pictures in streptococcal infections, and that renders their course, to say the least, kaleidoscopic.

Thus in addition to frequency there are imperative reasons for the interest which streptococcic infections command from the pediatrician, reasons which stem from the protean clinical manifestations of the disease, from epidemiologic considerations and from responses to serologic and chemical therapy. Despite great advances in the knowledge of streptococci and their relation to disease, they still offer inviting opportunities for study to the bacteriologist, the clinical epidemiologist, the allergist, the therapeutist and the health officer.

NOMENCLATURE AND NOSOGRAPHY

Consideration must first be given to nomenclature and nosography.[3] We have achieved some clarification of thought from consideration of tuberculosis. The names that will be applied to the various types of streptococcic infection are suggested in part by current practice for diseases due to the tubercle bacillus, since streptococcic diseases and tuberculosis are analogous in many respects. However, our observations are intended to stimulate thought along this line, not to be taken as statements of established fact.

There was a time when certain clinical conditions which are now recognized as tuberculosis were regarded as quite different diseases. It is now known that these conditions are clinical responses to infection with the tubercle bacillus, which vary according to the age of the patient and the relation to previous infection, to the type of tissue involved or to diverse strains and properties of the organism. So similar to the natural history of tuberculosis is infection with streptococci that to begin we might appropriately and conveniently designate infection with the latter organisms as "streptococcosis"—a term suggested by Dr. Sidney Sinclair.

Again as in tuberculosis, the matter of first infection and of reinfection with streptococci may be considered as of paramount importance in determining the reaction of the patient to infection. Briefly, in tuber-

2. Longcope, W. T.: Problems Relating to the Invasive Properties of Hemolytic Streptococci and Their Control by Sulphanilamide, Am. J. M. Sc. **195:** 577 (May) 1938.

3. Streptococcosis, Streptococcal Fever and Scarlet Fever, editorial, Connecticut State M. J. **6:**118 (Feb.) 1942.

culosis first infection is characterized if in the lungs by a diffuse exudative lesion associated with involvement of the regional lymph nodes; the lesions may progress, and death sometimes occurs in a relatively short time from generalized tuberculosis or from tuberculous meningitis. Recovery generally occurs without severe anatomic injury. If recovery takes place and there is reinfection, either endogenous or exogenous, the pulmonary lesion then tends to be circumscribed in the apical region, and the disease usually runs a chronic or subacute course, with the production of fibrous tissue and at times with cavitation; the regional lymph glands are but slightly involved, and there is little tendency to general invasion of the body.

In the natural history of streptococcosis a somewhat analogous pattern is disclosed. In our study we have observed that during the first three years of life especially, but not exclusively, there are a large

TABLE 1.—*Morbid Categories of Streptococcosis According to Site of Principal Lesion and Age of Patient*

A.	**Upper respiratory tract**
	Streptococcic fever
	1. Childhood type—largely in children under 3 years
	2. Intermediate type with rash (scarlet fever)—largely in children from 3 to 10 years
	3. Adult type—largely in persons over 10 years
B.	**Skin, glands, viscera, meninges, blood (may be associated with categories under A; may affect patients of any age)**
	Erysipelas, cellulitis, pyoderma
	Pneumonia, empyema
	Peritonitis, vaginitis
	Meningitis
	Bacteremia

number of children who have fever, pharyngitis, nasal discharge, persisting cervical adenitis, catarrhal otitis media and anemia. They are querulous, miserable appearing and anorexic, but their reaction to the infection is not usually stormy. The patients are subacutely ill from four to six weeks and are not their "usual selves" for a much longer time. Most of these children have hemolytic streptococci in cultures of material from the nose and throat, and of pus if there is suppuration of glands or ears. Invasion of the blood stream and metastatic foci sometimes occur. The effect of the infection may be described as low grade and general. Sulfanilamide usually lowers the temperature and prevents suppuration; nevertheless, the disease runs its six week course. For this syndrome one of us (D.C.D.) some years ago proposed the term "streptococcal fever," and the members of our clinic have found the designation a useful label. "Streptococcic fever, childhood type," designates our present conception (tables 1 and 2).[3]

In contrast, one observes acute tonsillitis in the older child and adult—usually a streptococcic infection and almost certainly not a first

infection. When uncomplicated, it is a disease usually characterized by stormy onset, often with chills and fever, sharp localization, frequently with follicular or diffuse exudate in the throat, and moderate transient adenopathy. The duration is a week or less when anatomic injury does not prevent rapid recovery. The most frequent complications are suppurative adenitis, peritonsillar abscess, otitis media, mastoiditis and bacteremia, but these occur less often than similar phenomena in infants with streptococcic fever; the disease in adults, in general, may be described as local. Perhaps this illness might be designated "streptococcic fever, adult type," since its incidence is greatest in patients more than 10 years of age, although it occurs also in younger children.

TABLE 2.—*Descriptive Outline of Categories for Patients from Whom Hemolytic Streptococci Were Cultured*

A.	Active streptococcosis, indicated by combined clinical and bacteriologic data. "Streptococcic fever" (hemolytic streptococci predominating respiratory pathogens in patients with pharyngitis, cervical adenitis or otitis media)
	1. Childhood type: under 3 years; low grade infection, rhinopharyngitis, moderate toxemia, generalized signs and symptoms; duration four to six weeks
	2. Adult type: over 10 years; acute infection, rhinopharyngitis, severe toxemia, localized signs; duration about one week
B.	Active streptococcosis, established by classic clinical data and confirmed by bacteriologic data
	Scarlet fever: 3 to 10 years (streptococcic fever with rash)
	Erysipelas: any age
C.	Active streptococcosis, established only by bacteriologic examination of blood or suppurative material
	Suppurative adenitis, otitis media, empyema, peritonitis, pyoderma, meningitis, bacteremia, etc.: any age; often associated with streptococcic fever, scarlet fever and erysipelas
D.	Latent streptococcosis. Presenting disease not considered streptococcic, but hemolytic streptococci cultured from nose or throat; "carriers"; "secondary invaders" (hemolytic streptococci often few in number and frequently associated with other respiratory pathogens)
E.	Acute glomerulonephritis
F.	Rheumatic fever (?)

We suggest that "streptococcic fever, childhood type," describes the usual clinical pattern of first or early infection with hemolytic streptococci. In our experience, infection with no other organism regularly follows the course described; hemolytic streptococci either are the only pathogens or are the predominating pathogens in cultures of material from the nose and throat; if there is suppuration of glands or ears—as occurred frequently before sulfanilamide therapy was developed—the organisms isolated from the pus belong in an overwhelming number of cases to Lancefield's group A, the "human" group, of hemolytic streptococci..[4] One must admit that the diagnosis of streptococcic

4. (*a*) Lancefield, R. C.: A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, J. Exper. Med. **57**:571, 1933. (*b*) Boisvert, P. L.: Human Hemolytic Streptococci from Diseases of Children, Am. J. Dis. Child. **59**:281 (Feb.) 1940. (*c*) Estrada, E.: The Lancefield Groups of Hemolytic Streptococci Found in Children, Yale J. Biol. & Med. **12**: 407 (March) 1940. (*d*) Higgins, N. R.: Hemolytic Streptococci from Common Skin Lesions of Children, Thesis, Yale University School of Medicine, 1941.

fever is made more definitely in retrospect than at the outset of the disease. Of course, first infections with hemolytic streptococci do not always follow the clinical pattern described. Sometimes, especially in very young infants, manifestation of disease consists merely of a mucoid nasal discharge (from which streptococci in practically pure culture are grown) without other symptoms. And, of course, erysipelas, peritonitis and empyema are seen in newborn infants. Here again the disease in the infant is clinically different from the form seen in the adult, owing perhaps, to some form of incomplete, transient inherited immunity. The reaction differs from that of adults in that there are less profound toxemia, a greater tendency to spread (in the case of erysipelas) and frequent invasion of the blood stream, especially in infants under 2 months of age;[5] the disease tends to be general in the infant and local in the older child or adult. "It is a well-established clinical fact that the age incidence of scarlet fever and erysipelas is almost the reverse the one of the other."[6]

When the signs of disease are similar, the differential diagnosis between a "first" infection with group A streptococci and a reinfection is not precisely defined. It would seem that the important differential points are general reaction and duration of illness. For example, in streptococcic fever, childhood type, with pharyngitis as the only physical sign of illness, the infant or child is subacutely "sick all over," so to speak, and will be so for six weeks or more. In contrast, the older child or adult with streptococcic pharyngitis—streptococcic fever, adult type—is likely to be sharply ill with sore throat and fever for a few days and thereafter, as a rule, he may be described as convalescent from the infection but not as subacutely ill with it. However, as mentioned before, in some of the infections which appear during the early days of life and are therefore almost surely first infections, no constitutional signs may appear.

Scarlet fever should be regarded, apparently, as a form of streptococcic fever intermediate between the childhood and the adult type. Cooke[7] has long held that the reaction to scarlatinal toxin is a unique form of bacterial allergy and suggests that the disease may depend on a previous infection with hemolytic streptococci. Certainly one rarely sees scarlet fever in infants, and Cooke has shown that the Dick test generally produces no reaction in newborn infants, even when their mothers are without natural antitoxin and react positively to the Dick test. In infants the Dick reaction usually becomes positive some time during the second year. In keeping with Cooke's measurement of sus-

5. Culotta, C. S.: Erysipelas in Children Under Two Years of Age, J. Pediat. **7**:16 (July) 1935.

6. Blake, F. G.: The Pathogenesis of Scarlet Fever and Erysipelas, Tr. Coll. Physicians Philadelphia **50**:27, 1928.

7. Cooke, J. V.: Scarlet Fever, in Barr, D. P.: Modern Medical Therapy in General Practice, Baltimore, Williams & Wilkins Company, 1940, vol. 2, p. 1501.

ceptibility to toxin and of the presence of antitoxin in the serum, the maximum incidence of scarlet fever is between the ages of 3 and 10 years; the absence of scarlet fever in early years is explained by lack of susceptibility to the toxin and in later years by the presence of antitoxin. From this point of view, scarlet fever may be regarded as a syndrome produced by a number of toxic reactions, such as fever, headache, nausea, vomiting and erythema, superimposed on the basic reaction to the streptococci. It seems that many children with mild scarlatinal manifestations react to the streptococcic infection in a subacute fashion resembling the childhood type of streptococcic fever. On the other hand, adults and older children tend to show a more violent localizing reaction, such as is exemplified in the adult type. Despite the striking features of scarlet fever, streptococcic fever, childhood type is, in our opinion, the most typical and the most frequent disease in children caused by hemolytic streptococci.

Turning now to the subject of "carriers," let us refer again to our paradigm, tuberculosis. Opie [8] stated that "recognition of the widespread occurrence of latent tuberculosis in children and in adults gives a broader basis for the investigation of the epidemiology of the disease. Since latent tuberculosis has been defined . . . as that unaccompanied by symptoms evident to the patient or by physical signs recognized by the physician, there are only two effective means by which tuberculous infection may be discovered, namely, by the tuberculin reaction and by characteristic changes in x-ray plates." Does a parallel condition exist in respect to streptococcosis? There seems to be a somewhat analogous group of patients in whose cases the presenting illness is not considered streptococcic but cultures of material from the nose and throat made at the time of admission to the hospital show the presence of hemolytic streptococci, often along with other respiratory pathogens. Also, there are children admitted to the hospital for some nonstreptococcic disorder whose cultures made on admission do not show streptococci but whose later cultures do show these organisms. Sometimes there develops in these patients evidence of streptococcic disease, and sometimes no such evidence appears. In certain cases the organisms were probably acquired in the institution from dust particles or droplets from the pharynx—"nosocomial infections." [9] In others the cultures made on admission simply failed to reveal the streptococci which were there.[10]

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8. Opie, E. L.: Infection with Tuberculosis in Children and in Adults: Mary Scott Newbold Lecture, Tr. Coll. Physicians Philadelphia **49**:24-47, 1927.

9. Wright, J.: Nosocomial Infections in Children's Wards, J. Hyg. **40**:647 (Dec.) 1940.

10. Coburn, A. F., and Pauli, R. H.: The Interaction of Host and Bacterium in the Development of Communicability by Streptococcus Hemolyticus, J. Exper.

(Footnote continued on next page)

The carrier state with respect to streptococci is perhaps the most important aspect of the subject—important alike for diagnosis in the individual case and for epidemiology. A positive result of culture without manifest streptococcic disease may represent in some cases a situation analogous to that of a typhoid carrier, who harbors the organisms and although not ill himself is dangerous to other persons. In other cases the situation seems analogous to that of a patient with latent tuberculosis, in whom also the organisms are harbored but a change in whose resistance may lead to active disease, although he was until that time of little danger to his contacts. At the present time we are obliged to continue to speak in terms of "latent" and "active" streptococcosis and of "sick" and "healthy" carriers of streptococci, with not too clear a conception of the clinical connotations of the words.

STATISTICAL STUDY OF STREPTOCOCCOSIS IN THE INPATIENT PEDIATRIC SERVICE OF THE NEW HAVEN HOSPITAL

The following study consists of a survey of streptococcosis in respect to certain clinical characteristics and to incidence in the public children's wards of a general hospital in a community of some 200,000 persons. We are well aware of the possibility that with a clientele of higher economic status or with a unit of different size or one located in a different climate, the magnitude and the characteristics of the problem might not be exactly the same.

We have gone over records of all children admitted to the pediatric inservice, for contagious and for noncontagious disease, of the New

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Med. **73**:551 (April) 1941. This is a most stimulating study of an epidemic of streptococcic infection in the Babies Hospital in New York. A pargaraph which is especially appropriate to this discussion of carriers may be quoted:

"Hemolytic streptococcus may or may not be infective. Carriers of this organism usually do not communicate disease and they may usually be considered harmless. This applies to most carriers throughout most of the year. Under at least three conditions, however, the carrier may communicate disease and must then be considered dangerous. These three conditions are: (*a*) a seasonal increase in general activity of hemolytic streptococcus, probably due to some climatic effect; (*b*) increased infectivity of the organism associated with virus infection of the host; and (*c*) increased infectivity of organisms established in the tissues of infants and children. The dangerous carrier usually becomes a harmless carrier within 2 months; however, he may again acquire the capacity to spread disease under one of the three conditions just mentioned. In our epidemic type 12 strain, development of the capacity to spread was dependent on the host, and was closely associated with the age of the patient. In the Babies Hospital epidemic, organisms colonizing in infants and toddlers were highly communicable, whereas those infecting the nurses were not. Furthermore, the infants had few or perhaps no recognizable type 12 organisms in their throat flora when they were spreading infection; whereas the nurses had type 12 in predominance, coughed and sneezed, yet were harmless. It seems therefore that the spread of infection could not be ascribed to the mere numbers of bacteria disseminated but would have to be explained by some peculiar quality of the agent for which we propose the term 'communicability.'"

Haven Hospital for six years. We analyzed records—4,849 in all—for three years, 1934, 1935 and 1936 (group I), before sulfanilamide and its derivatives came into use, and those for three years, 1938, 1939 and 1940 (group II), after the drugs were well established in treatment (table 3). The year 1937, in the course of which sulfanilamide came into use, was for that reason omitted.[11] Sick children from birth to 16 years old are admitted to our wards, and most of them except premature infants and some newborn babies transferred from the maternity ward have routine cultures of material from the nose and throat and of blood done on admission; for many of these patients cultures are repeated. We have grouped and subgrouped patients according to various criteria: children with and without active streptococcic disease who had hemolytic streptococci in the nose, throat or blood on admission or later; children

TABLE 3.—*Statistical Summary Relative to Cultures of Material from Nose and Throat in Children's Clinic, New Haven Hospital (1934 to 1936 Group I, 1938 to 1940 Group II)*

	Group I	Group II
Total patients admitted	2,037	2,812
Patients having cultures of material from nose and throat	1,862	2,686
Ratio to total patients admitted	91%	96%
Patients having no hemolytic streptococci in nose, throat or lesion	1,409	2,069
Patients having hemolytic streptococci in nose, throat or lesion	453	617
Ratio to patients who had cultures	24%	23%
Patients having active streptococcosis	251 *	415 †
Ratio to patients who had cultures	13%	15%
Patients having hemolytic streptococci but no streptococcic disease	202	202
Ratio to patients who had cultures	11%	8%

* The following patients without cultures yielding hemolytic streptococci are included: 4 with scarlet fever, 1 with surgical scarlet fever and 9 with erysipelas.
† The following patients without cultures yielding hemolytic streptococci are included: 1 with scarlet fever and 5 with erysipelas.

who had no laboratory evidence of streptococci but who had a well recognized streptococcic disease; children with acute glomerulonephritis, and children with rheumatism. Nose and throat cultures were not considered separately. These data are classified in table 4.

Over 90 per cent of the patients in our wards (table 3) had cultures of material from the nose and throat on blood agar plates (91 per cent of group I; 96 per cent of group II). A number of patients also had cultures of material from various suppurative lesions. From the resulting data it was disclosed that in this series 1 out of every 4 patients who had cultures made on admission to the clinic (24 per cent of group I; 23 per cent of group II) had hemolytic streptococci in the nose or

11. It would seem possible that because of the efficacy of chemotherapy the physician of the near future will know from first hand observation as little of the natural history of streptococcic disease as he does now of diphtheria, typhoid and rickets, of which many of the present generation of physicians have seen little in some localities.

throat or in a lesion. And correlation of the results of the cultures with clinical data revealed that 13 per cent of the patients of group I and 15 per cent of the patients of group II had active streptococcosis. Thus, on the average, 10 per cent of the patients in the service in these six years did not seem to have active streptococcosis but were bearers or acquirers of streptococci at some time while they were in the hospital.

TABLE 4.—*Nosocomial Statistics of Patients in Groups I and II from Whom Hemolytic Streptococci Were Cultured or Who Had Classic Streptococcosis*

Organisms found in cultures of material from nose or throat on admission	Number of Patients			
	Group I		Group II	
Streptococcic fever, tonsillitis and laryngitis	57		157	
Classic clinical streptococcosis				
Scarlet fever	32		107	
Surgical scarlet fever	3		3	
Erysipelas	10		7	
Streptococcosis bacteriologically established from a lesion	61		66	
Streptococcosis and glomerulonephritis	5		5	
Total, hemolytic streptococci accepted as etiologic agent		168		345
Glomerulonephritis without other evidence of streptococcosis	1		5	
Rheumatism, chorea	16		25	
Latent streptococcosis (a)	156		145	
Total hemolytic streptococci cultured on admission from nose and throat	341		520	
Organisms found in later cultures				
Scarlet fever	1	1	2	2
Erysipelas	1	1		
Glomerulonephritis	1	1	1	1
Suppurative lesions			4	4
Rheumatism, chorea	6		19	
Latent streptococcosis (b)	37		14	
Organisms not present in nose or throat but found in a suppurating lesion	66 *	66	57 †	57
Total, patients having hemolytic streptococci in nose, throat or lesion	453		617	
Organisms not isolated				
Scarlet fever		4		1
Surgical scarlet fever		1		
Erysipelas		9		5
Total, patients with active streptococcosis		251		415

† Group contains 1 patient with scarlet fever, 3 with surgical scarlet fever and 3 erysipelas and 1 with glomerulonephritis associated with suppurative mastoiditis.
† Group contains 1 patient with scarlet fever, 3 with surgical scarlet fever and 3 with erysipelas.

The children in this group suffered from a variety of illnesses, such as diabetes, asthma, bronchitis, diphtheria, blood dyscrasias, rheumatism and behavior and feeding disorders. For the most part, these patients may, as I have already indicated, be regarded as having latent streptococcosis. To what extent the streptococci were accomplices in causing the illness or illnesses from which the child suffered is a most important problem. One example may be cited. A little boy with diabetes was admitted repeatedly because regulation with diet and insulin was difficult. Sometimes he had a slight fever and possibly, on occasion, a mild pharyngitis; he always had streptococci in his nose or throat but never

a condition which all would agree was active streptococcosis. To what extent were streptococci responsible for the child's difficulty in handling his diabetes? One would like the facts on which to make that appraisal, but they are not available at this time.

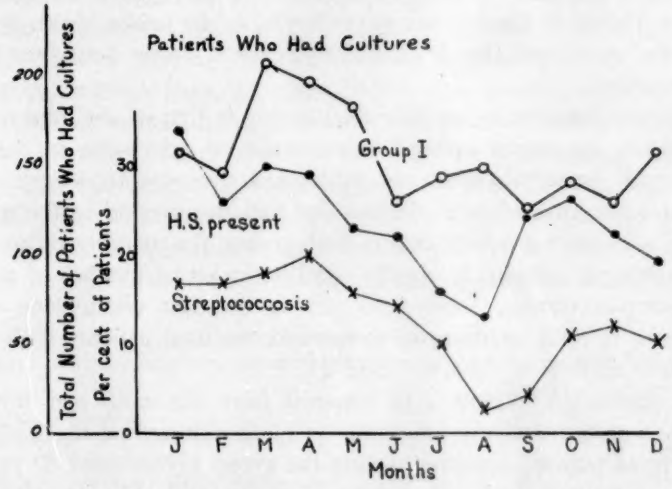


Chart 1.—Monthly proportion of patients of group I for whom cultures were made who had streptococcosis or were carriers of hemolytic streptococci.

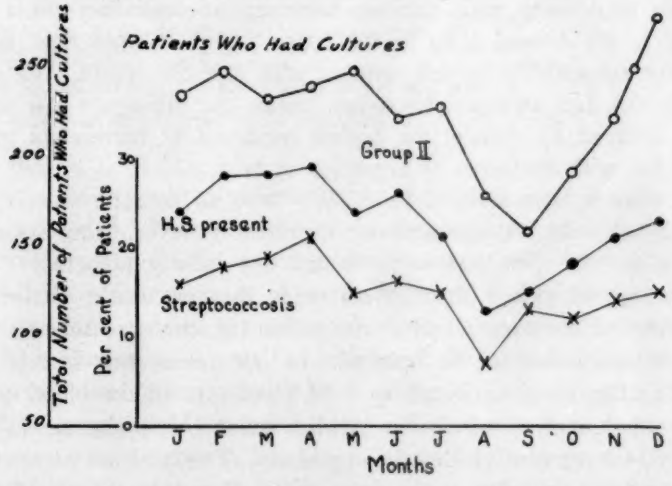


Chart 2.—Monthly proportion of patients of group II for whom cultures were made who had streptococcosis or were carriers of hemolytic streptococci.

Streptococcosis is a year round disease in New Haven but with a predilection for the winter months; in our series there were a greater number of persons with streptococcosis and of persons harboring hemolytic streptococci admitted to the hospital during the fall, winter

and spring quarters than during the summer (charts 1 and 2). One can find in the wards at almost any time a case of streptococcic disease to discuss with students—something we in our clinic can hardly say with respect to any other disorder! So for the diagnosis for the individual patient it is important to realize that the streptococcus does not disappear in New Haven in the summer time, but from the public health point of view the significant fact is that this organism really flourishes in the cool months.

Another interesting monthly relationship is that of the total number of patients for whom cultures were made on admission to the total number of patients (with and without active streptococcic disease) who at some time while in the hospital had streptococci in the nose or throat or in pus; one finds that in both groups the monthly ratios (with one exception, January, group I) parallel the actual number of patients with streptococcosis. There was thus a constant relationship month by month of total incidence of streptococci to total patients with actual streptococcic disease (charts 1 and 2).

In addition to cultures of material from the nose and throat, a majority of our patients have one or more cultures of the blood—62 per cent of patients admitted during the group I years and 80 per cent of those admitted during the group II years (table 5). Despite fewer patients who had blood cultures and fewer with active streptococcosis during the group I period than during the group II period, there were in total many more patients with streptococcic bacteremia (2.57 times) in the former than in the latter group—14 per cent and 3.3 per cent respectively of the patients with streptococcosis. We cannot explain this fact to our satisfaction. Since the difference can scarcely have occurred by chance, the higher incidence of bacteremia may be associated with attributes of organism or host, which, as is well recognized, change from time to time. We have no data for discussion of these possibilities. Analyses of our statistics, however, bring out certain facts which are pertinent even though not fully explanatory.

One would expect that sulfanilamide therapy would diminish the incidence of bacteremia after institution of that treatment on the patients' admission to the hospital. In our series, this fact is established (table 5), since in group I 44.4 per cent of the blood cultures made subsequent to admission yielded streptococci whereas in group II only 14.3 per cent yielded the organisms. The facts are more striking than the figures suggest, for there were only 2 such bacteremias in group II; one was demonstrated on the second day in the hospital, and the other was noted post mortem in a patient with infantile cerebral palsy who had had unexplained fever, had had two blood cultures which had not yielded streptococci and had not had chemotherapy.

But of the 36 patients in group I with bacteremia, 20 had positive results of cultures on admission, which is 8 per cent of the number

of patients with streptococcosis in that group. In contrast, of the 14 patients in group II with bacteremia, 12 had positive results of cultures on admission, and these constitute only 2.8 per cent of the number of patients with streptococcosis in that group. Here also one naturally thinks of sulfanilamide, for if the drug was given by referring physicians before the patients were sent to the hospital it is likely that the number of blood cultures yielding the organism on admission would be few. We cannot establish from our records that this actually occurred, but it is a fact that sulfanilamide is freely given as a panacea for all sorts of febrile disorders, some of which turn out to be streptococcic.

The difference might in some measure be related to the duration of the illness prior to admission to the hospital; of the patients whose cultures yielded streptococci at that time, 50 per cent of those in group I and 25 per cent of those in group II had been ill for a week and longer.

TABLE 5.—*Blood Cultures*

	Group I	Group II
Total patients admitted	2,037	2,812
Patients having blood cultures	1,267	2,244
Ratio to patients admitted	62%	80%
Patients with active streptococcosis	251	415
Patients having hemolytic streptococcus bacteremia	36	14
Ratio to patients with streptococcosis	14%	3.3%
Patients having hemolytic streptococcus bacteremia on first day in the hospital	20	12
Ratio to patients with streptococcosis	8.0%	2.8%
Ratio to total patients with bacteremia	55.5%	85.7%
Patients having hemolytic streptococcus bacteremia after culture on admission	16	2
Ratio to total patients with bacteremia	44.4%	14.3%
Patients with bacteremia on admission ill longer than one week	10	3
Ratio to patients with bacteremia on admission	50%	25%

Other data regarding patients with bacteremia on admission are shown in table 6. Early bacteremia is characteristic of erysipelas in young children but occurs in scarlet fever usually only later and with complications. Therefore, it is of interest to find that there is a quantitative difference in the forms of streptococcosis with bacteremia detected on admission, in that the proportion of patients with the suppurative complications of scarlet fever is greater in group I (25 per cent) than in group II (8.3 per cent). This point is of importance only because scarlet fever in the group II years was frequently treated by general practitioners with sulfanilamide from the time the diagnosis was made; and of all forms of streptococcosis scarlet fever is the one usually recognized early.

In regard to cutaneous infections with bacteremia detected on admission, the situation apparently is the reverse of that for scarlet fever, there being relatively more in group II than in group I; the number of patients is too small, however, to justify deductions (table

6). The incidence of other forms of streptococcosis with bacteremia is much the same in the two groups.

Lastly, a study of the distribution of patients who had bacteremia on admission into age periods showed a similar pattern of scattering in the two groups; hence age does not seem an important factor in explaining the differences.

TABLE 6.—*Patients with Bacteremia on Admission*

Presenting Clinical Diagnosis	Group I		Group II	
	Number	Per Cent	Number	Per Cent
Cutaneous infections	1	5	2	16.60
Scarlet fever with suppurative complications	5	25	1	8.35
Mastoiditis without scarlet fever	4	20	3	25.00
Meningitis	2	10	..	.....
Diarrhea in newborn	1	5	1	8.35
Streptococcic fever	..	....	1	8.35
Erysipelas	4	20	3	25.00
Peritonitis	1	5	..	.....
Congenital cardiac disease	1	5	..	.....
Suppurative arthropathy	1	5	1	8.35
Total patients with bacteremia	20	100	12	100.00
Patients with active streptococcosis	251		415	

TABLE 7.—*Nosocomial Incidence for Each of Six Years of Patients with Active Streptococcosis*

1934	1935	1936	Total		Total	1938	1939	1940
5	10	14	29	Streptococcic fever	106	26	46	34
7	11	6	24	Tonsillitis	47	17	13	17
4	0	0	4	Laryngitis	4	3	0	1
14	11	13	38	Scarlet fever	111	29	35	47
2	2	1	5	Surgical scarlet fever	6	0	4	2
5	11	9	25	Erysipelas	15	8	2	5
11	17	8	36	Bacteremia	14	4	6	4
3	12	8	23	Suppurative cervical adenitis	21	5	10	6
12	12	25	49	Suppurative otitis media	65	18	29	18
10	7	9	26	Mastoiditis	8	4	1	3
0	1	0	1	Sinus thrombosis	1	0	0	1
0	0	1	1	Abscess of the brain	3	2	1	0
3	5	2	10	Meningitis	3	1	1	1
2	2	7	11	Retropharyngeal abscess	1	0	1	0
3	2	3	8	Peritonsillar abscess	4	2	1	1
5	3	7	15	Pyodermia: cellulitis	28	6	9	13
2	2	1	5	Suppurative axillary adenitis	4	1	3	0
0	0	0	0	Suppurative inguinal adenitis	1	0	0	1
1	1	0	2	Paronychia	3	1	1	1
3	4	1	8	Empyema	7	2	0	5
1	0	0	1	Sinusitis	1	0	0	1
1	0	0	1	Pericarditis	1	0	1	0
1	2	2	5	Peritonitis	0	0	0	0
1	0	0	1	Suppurative arthropathy	1	0	0	1
0	1	0	1	Purulent conjunctivitis	1	0	0	1
0	0	0	0	Panophthalmitis	1	0	0	1
0	1	0	1	Pyuria	2	0	0	2
0	0	0	0	Vaginitis	5	0	0	5

A list of a few important diseases in the six years with totals for the two groups is now presented; the diseases are divided roughly into streptococcic fever, with which tonsillitis and laryngitis are considered, classic streptococcosis and suppurative lesions (table 7).

The patients with the childhood type of streptococcic fever are somewhat arbitrarily demarcated from those with tonsillitis, i. e., the adult type of streptococcic fever, in the survey of our past hospital histories, because our present conception of streptococcosis was not held throughout the period covered by these statistical analyses; in the future our histories should furnish more accurate differential data. But the age incidence and the characteristic clinical picture as we now appraise it are actually different, as already stated, for the two conditions. Laryngitis may be associated with streptococcic fever and with tonsillitis. If the three conditions are taken together, the resulting combination contributes the largest single number of patients in either group; scarlet fever is a close second, and the ratio of scarlet fever to streptococcic fever in group I (1:1.3) is the same as that in group II. There is an important age differentiation here, however, streptococcic fever being at least six times as common as scarlet fever in children under 3 years of age and only twice (1.8) as frequent in patients from 3 to 11 years —a period when over one half of the reported cases of scarlet fever occur.[12]

Streptococcic laryngitis is an uncommon disorder in our clinic; in most of our cases laryngitis is associated with the influenza bacillus or the pneumococcus; the possibility of a virus causation is always to be considered.

Four per cent of the admissions in group II were for scarlet fever, and less than 2 per cent (1.8 per cent) of those in group I. Cooke and others have called attention to the apparent increase in the incidence of this disease, which varies greatly in both severity and mortality. Hemolytic streptococci were demonstrated in cultures of material from the nose and throat (table 4) on admission for 84 per cent of the patients with scarlet fever in group I and for 96 per cent of those in group II —the increase in positive results in the latter group probably being due to better technical procedures. Since the ratios of patients with streptococcosis (about 13 per cent) and of all streptococcus bearers (about 23 per cent) to patients admitted were, as already shown, the same respectively in the two groups (charts 1 and 2 and table 3), we were not prepared to find that the relative incidence of scarlet fever in group II was over twice that in group I; the morbidity of this disease is usually considered a reliable index of the prevalence of hemolytic streptococci in a population unit. Our groups, of course, were composed of hospitalized patients and by virtue of that fact are selective; however, the ratio of the number of patients with scarlet fever in the group II years to that in the group I years (2.7) is almost exactly the same (2.8) as the ratio which existed between the totals of cases officially

12. In the age period 10 to 16 years there were few admissions for streptococcosis; this situation may obtain because the morbidity is low or because the patients are cared for at home or for both reasons, as seems most probable.

reported to the department of health of New Haven in the two periods.[13] Of course, we do not know whether the incidence of streptococcus carriers was constant during these years in New Haven as it was in our hospital.

The favorable influence of sulfanilamide on streptococcosis is strikingly shown in the low incidence of operative mastoiditis and of meningitis in group II, although there were many patients with suppurative otitis media; this is a remarkable demonstration of the effectiveness of therapy with sulfanilamide or one of its derivatives. No special explanation comes to mind to account for the discrepancy between 19 patients with pharyngeal abscess in the smaller group I and only 5 in group II. Chemotherapy does not seem to furnish the complete answer, since such lesions are often present when the patients are admitted.

Special attention should be called to the 5 patients with vaginitis in 1940. Actually we had 10 such patients in that year, since there were 5 additional ones seen in the outpatient service or private practice. DeWaal[14] recorded 22 cases in a series of 2,169 cases of scarlet fever. Hardy[15] recovered streptococci of group A from the vagina twenty-eight times in 12 cases. This condition apparently may be a definite clinical entity, which we did not recognize as such prior to 1940. The patients varied in age from 13 months to 13 years. The disease sometimes occurred without constitutional symptoms; frequently it was a part of some other form of active streptococcosis, and in other instances it seemed to exist as the only manifestation of streptococcic infection. The disease was characterized by dysuria, slight discharge and a genital inflammatory reaction comparable to that seen in the pharynx. Two patients had peroneal erysipelas, 2 others had scarlet fever and 4 had streptococcic fever. Hemolytic streptococci in almost pure culture were grown from the vagina of each patient; the organisms were from 9 patients of group A and those from 1 were of group B. The latter patient had no constitutional symptoms. Hemolytic streptococci of group A were obtained by pharyngeal culture from 4 patients.

Cutaneous abrasions are potential portals of entry for streptococci, from which in many cases pyodermia develops. Fingers are important, since they may become infected with streptococci from the mouth, and paronychia, erysipelas or cellulitis of some variety may result. A surprising number of patients with chronic eczema are infected with streptococci, as are many persons with dermatoses between the toes and back of the ears; such infections were associated with bacteremia in

13. Bearg, P. A.: Personal communication to the author.

14. DeWaal, H. L.: The Serological Types of Haemolytic Streptococci in Relation to the Epidemiology of Scarlet Fever and Its Complications, J. Hyg. **40**: 172 (March) 1940.

15. Hardy, G. C.: Vaginal Flora in Children, Am. J. Dis. Child. **62**:939 (Nov.) 1941.

some of our patients. Higgins [4d] found that the streptococci from a series of 40 patients with impetigo and eczema belonged to group A in all instances.

Combined data for both groups regarding erysipelas are presented in table 8. The material is not unusual, but attention is called to the fact that 45 per cent of the patients under 2 months of age with erysipelas had hemolytic streptococci in the nose and throat. This fact definitely points to the occurrence of streptococcic fever even

TABLE 8.—*Patients with Erysipelas*

Age	Total Patients	Material from Nose and Throat Culture		Bacteremia	Outcome	
		Positive	Negative		Died	Recovered
Under 2 mo.	11 *	5	6	7	3	8
2 mo.-1 yr.	6 †	3	2	1	1	5
1 yr.-2 yr.	4	1	3	1	1	3
2 yr.-16 yr.	19 ‡	9	9	0	0	19
Total	40	18	20	9	5 §	35

* Seven of these in group I.
† One patient (6 months) did not have a culture.
‡ One patient (14 years) did not have a culture.
§ Four of these in group I.

TABLE 9.—*Patients with Acute Glomerulonephritis*

	1934	1935	1936	Group I	Group II	1938	1939	1940
Cultures of material from nose, throat or lesions yielding hemolytic streptococci on admission								
With demonstrated streptococcosis	4	1	2	7	5	5	..	..
Without other evidence of streptococcosis	..	..	1	1	5	1	2	2
Percentage of patients with hemolytic streptococci on admission				50%	52%			
Later cultures yielding hemolytic streptococci	1	..	..	1	1	1	..	..
No hemolytic streptococci demonstrated	..	4	3	7	8	3	3	2
Total number of patients	5	5	6	16	19	10	5	4

in very young babies and of the pharynx as a source of infection in erysipelas; this would seem to be particularly likely in cases of the facial variety. Although there were many more patients with streptococcosis in group II than in group I, there were only 15 patients with erysipelas in group II, in contrast to 25 in group I.

As shown in table 9, hemolytic streptococci were present in the nose and throat on admission in 50 per cent of the patients in both groups suffering from acute glomerulonephritis, regardless of the stage of the disease when they entered the hospital and regardless of other evidences of streptococcosis. We do not have adequate data to justify

a statement on the efficacy of sulfanilamide therapy in the treatment of acute glomerulonephritis; other writers have reported successful results.[16]

Our observations on rheumatic fever, chorea and rheumatic cardiac disorders, are recorded in table 10. They demonstrate that without regard to duration of disease or character of the symptoms 26 per cent of the patients with these conditions in group I and 30 per cent of those in group II had hemolytic streptococci in the nose and throat on admission to the clinic. Further, 36 per cent of those in group I had streptococci in the nose and throat at some time during the course of their hospitalization, and, similarly, 54 per cent of those in group II.

Our study of mortality is shown in tables 11 and 12. It is at once obvious that as regards life the presence of bacteremia in streptococcosis

TABLE 10.—*Patients with Rheumatism or Chorea*

	1934	1935	1936	Group I	Group II	1938	1939	1940
Cultures of material from nose, throat or lesion yielding hemolytic streptococci on admission	5	10	1	16	25	12	6	7
Percentage of patients with hemolytic streptococci on admission				26%	30%			
Later cultures containing hemolytic streptococci	4	1	1	6	19	4	7	8
Hemolytic streptococci present in nose and throat at some time	9	11	2	22	44	16	13	15
Percentage of patients with hemolytic streptococci present at some time				36%	54%			
No hemolytic streptococci demonstrated	3	20	15	38	37	16	8	13
Total number of patients	12	31	17	60	81	32	21	28

is the most ominous of all signs. In group I, 87 per cent of patients who died had bacteremia and 58 per cent of all patients who had bacteremia died. In group II the figures are quite different, probably because of sulfanilamide; 50 per cent of the patients who died had bacteremia, and 21 per cent of all patients who had bacteremia died.

The mortality rates for the two groups are 9.6 per cent and 1.4 per cent respectively, the difference undoubtedly being due in large measure to chemotherapy; the rate in 1935 was high, 15 per cent, and in 1938, 0.

Meningitis ranks high as a cause of death in group I, being usually associated with suppurative mastoiditis requiring operation. The latter condition, as previously pointed out, is greatly reduced in incidence by the use of sulfanilamide.

16. Williams, R. H.; Longcope, W. T., and Janeway, C. A.: The Use of Sulfanilamide in the Treatment of Acute Glomerulonephritis, Am. J. M. Sc. **203**: 157 (Feb.) 1942.

In the past, empyema caused by hemolytic streptococci was an important factor in mortality from streptococcic infection. In a series of 31 cases prior to 1937 which one of us [17] has reported the rate was 58 per cent. We have had 15 patients with empyema since sulfanilamide was introduced, with only 2 deaths. A child in 1939 died with rheumatic

TABLE 11.—*Mortality from Streptococcosis*

	Group I	Group II
Patients	251	415
Deaths	24	6
Mortality rate	9.6%	1.4%
Patients with bacteremia who died	21	3
Bacteremia rate for patients who died	87%	50%
Patients without bacteremia who died	3	3
Patients with bacteremia	36	14
Mortality rate for patients with bacteremia	58%	21%

TABLE 12.—*Data Regarding Patients with Active Streptococcosis Who Died in the Six Years Covered by the Study*

	Group I			Group II		
	1934	1935	1936	1938	1939	1940
Patients	70	90	91	110	154	151
Deaths	6	14	4	0	3	3
Mortality rate	8.7%	15%	4.5%	.....	1.9%	2%
Cervical adenitis (bacteremia)	1	.....	.....	.....	.....	.....
Bacteremia	.....	2	.....	.....	.....	.....
Meningitis and erysipelas (bacteremia)	2	1	.....	.....	.....	.....
Mastoiditis (bacteremia)	1	1	.....	.....	.....	.....
Pneumonia (bacteremia)	1	.....	.....	.....	.....	.....
Cellulitis (bacteremia)	1	.....	.....	.....	.....	.....
Meningitis (bacteremia)	.....	3	.....	.....	.....	.....
Peritonitis (bacteremia)	.....	2	1	.....	.....	.....
Erysipelas (bacteremia)	.....	2	1	.....	.....	.....
Empyema (bacteremia)	.....	1	.....	.....	.....	.....
Empyema	.....	2	.....	.....	.....	.....
Scarlet fever (bacteremia)	.....	.....	1	.....	.....	.....
Mastoiditis; meningitis	.....	.....	1	.....	.....	.....
Newborn, meningocele, meningitis (bacteremia)	.....	.....	.....	.....	1	.....
Rheumatic cardiac disease, hemolytic streptococcic pericarditis and empyema	.....	.....	.....	.....	1	.....
Quadriplegia (P. M. bacteremia)	.....	.....	.....	.....	1	.....
Erysipelas of newborn (bacteremia) one day treatment	.....	.....	.....	.....	.....	1
Diarrhea of newborn (bacteremia)	.....	.....	.....	.....	.....	1
Scarlet fever and empyema (no chemotherapy)	.....	.....	.....	.....	.....	1

heart disease and also had hemolytic streptococcus empyema terminally, and one in 1940 did not have an accurate diagnosis made and was not treated with the drug; both patients, therefore, are recorded in group II. There were 3 deaths from empyema in the patients of group I.

17. Powers, G. F.: Chemotherapy in the Treatment of Streptococcus Empyema in Children, Internat. Clin. **2**:131 (June) 1941.

The circumstances in regard to the 6 deaths in group II are such that only 1, that of the child with empyema just referred to, could conceivably have been prevented by therapy; the other children who died were moribund on admission to the clinic or the streptococci came in to deal the death blow in an already hopeless condition.

SUMMARY AND CONCLUSION

In summary, we may emphasize a few facts brought out by a study of records of 4,849 patients, newly born to 16 years old, admitted to the inpatient service of the children's clinic of the New Haven Hospital; 2,037 patients were in group I—admitted in three years prior to chemotherapy with sulfanilamide and its derivatives—and 2,812 in group II—admitted in three years since. The data show that 1 of 7 patients had active streptococcosis, and in 1 of 4 patients hemolytic streptococci were present in the nose or throat, in a suppurative lesion or in the blood; in some of these patients the presenting disease seemed to bear no direct relationship to this organism. This condition may be termed latent streptococcosis.

In New Haven, hemolytic streptococci are important pathogens in each month of the year, but infections seem most prevalent in March and April and other cool months and least prevalent in August.

Of the patients with active streptococcosis those with streptococcic fever of the childhood type (which we regard as a clinical entity) and with scarlet fever constituted the largest percentages; the former disease is at least six times as frequent as the latter in children under 3 years, although the ratio thereafter (to the eleventh year) is 2 to 1. Streptococcic fever of the childhood type suggests in many ways a "first" infection with streptococci in the same sense that childhood tuberculosis is the type of primary infection with tubercle bacilli; the disease is the typical streptococcic infection of childhood. Scarlet fever is perhaps a manifestation of a special allergic condition in a child who has had streptococcic fever. Follicular tonsillitis is the typical reinfection type of disease and may be considered streptococcic fever of the adult type.

Suppurative otitis media was a common manifestation of streptococcic infection in both our groups, but owing to the use of sulfanilamide operative mastoiditis and meningitis were strikingly diminished in group II.

Bacteremia is a characteristic of a large majority of the children who die of streptococcosis.

The general mortality of patients with streptococcosis in group I was 9.6 per cent, and of patients in group II, 1.4 per cent, with no deaths in one of the years studied.

789 Howard Avenue.

Obituaries

HENRY DWIGHT CHAPIN, M.D.
1857-1942

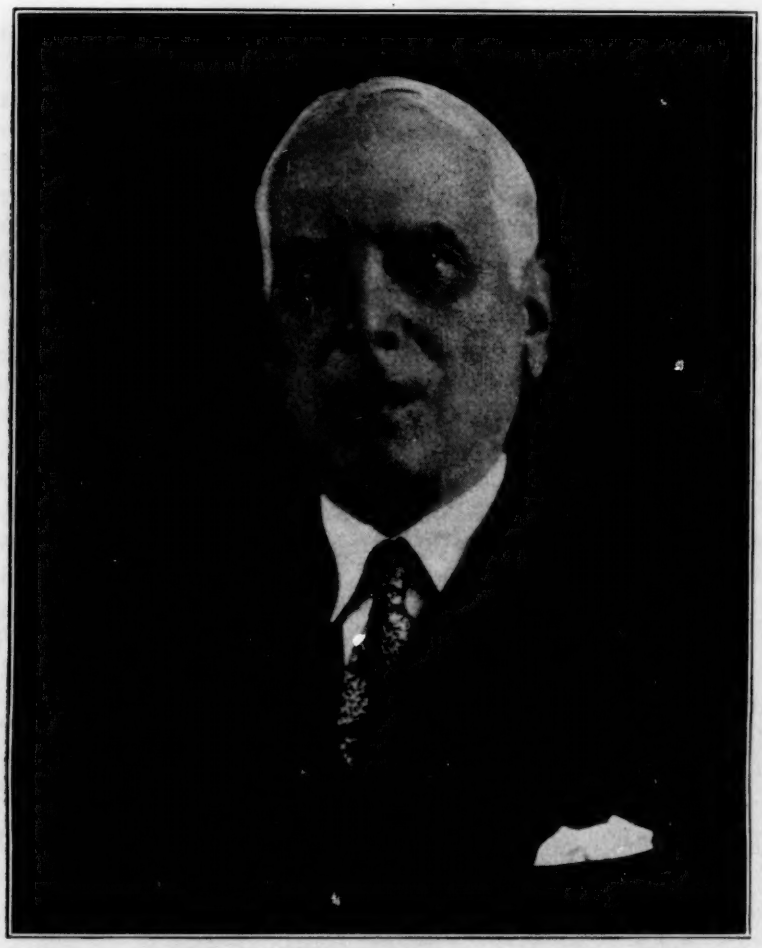
Dr. Henry Dwight Chapin died in the early morning of June 28, 1942 at his home in Bronxville, N. Y., in his eighty-fifth year.

He was born in Steubenville, Ohio, on Feb. 4, 1857. As was the case with most ministers' families of that day, the Chapins lived in various communities, including Trenton and Princeton, and finally settled permanently in the city of New York when Henry was about 14 years old. He attended a famous secondary school for boys, the Chapin Collegiate School, which was established by his father. He graduated from Princeton University with the class of 1877 and from the College of Physicians and Surgeons (now merged with Columbia University) in 1881. Dr. Chapin joined the New York Post-Graduate Medical School and Hospital as professor of pediatrics in 1886 and continued his close connection with the babies' wards and with the hospital as a member of the board of directors until his death. In 1888 he became a charter member of the American Pediatric Society, of which he was president in 1910. He was chairman of the New York State Reconstruction Commission in 1919 and was president of the Child Welfare Federation in 1924. Dr. Chapin was several times chairman of the pediatric section of the New York Academy of Medicine and was chairman of the pediatric section of the American Medical Association in 1912-1913. The local, state and national medical societies received his loyal support throughout his entire medical career. Membership in the Society of Mayflower Descendants, the Society of Colonial Wars and the Century Club was perhaps an index of his interests outside of medicine. In 1933 he was awarded the Columbia University medal for "outstanding contributions to problems relating to the care of children and as a pioneer in hospital social service."

Dr. Chapin was the founder of the Speedwell Society. He was an attending physician for many years in the babies' wards of the New York Post-Graduate Medical School and Hospital and at the Willard Parker and Riverside Hospitals and was consulting physician at the Randall's Island Hospital, St. Agnes Hospital at White Plains, N. Y., the Convalescent Home for Children at Sea Cliff, N. Y., and the Hackensack (N. J.) Hospital.

Dr. Chapin's contributions to medical literature were extensive and vital. Perhaps his best known books so far as the medical profession is concerned are "The Theory and Practice of Infant Feeding," his textbook "Diseases of Infants and Children," written in collaboration

with Dr. Godfrey R. Pisek, and his "Pediatrics," of which he was the co-author with Dr. L. T. Royster. "The Theory and Practice of Infant Feeding" went through three editions and the "Diseases of Infants and Children" through four editions and six reprintings. His popular essays titled "Vital Questions" were published in 1902 and are perhaps



HENRY DWIGHT CHAPIN, M.D.

1857–1942

This photograph was taken at about the time of his seventy-fifth birthday.

the most significant of his writings, in that they define the relationship of the physician to the social problems of the community, an interest which came to occupy a large part of his professional life. "Health First: The Fine Art of Living" appeared in 1917, and "Heredity and Child Culture" was first printed in 1922 and reprinted in 1928.

Besides these volumes there were many articles appearing in medical journals, having to do mainly with problems of hospitalization, infant feeding and the social aspects of medicine, especially as they related to children. Dr. Chapin taught a simple form of milk modification, as witness his writings and the Chapin dipper; but from the beginning he stressed the fact that milk was a biologic fluid and that other types could be made to have no more than a superficial resemblance to mother's milk, and that calories could never be more than a measure of fuel values and told nothing as to the suitability of a substance as a food. That he was quick to grasp the importance of a new agent for feeding was shown by his prompt request to duplicate at a reasonable cost a new sugar brought from Germany—a request that resulted in the manufacture of Dextri-Maltose, the first samples of which were tried out under his direction in the babies' wards. Clean milk, sanitary housing, the home hospital and finally the removal of the sick infant out of the hospital and into a good home at the earliest possible moment seem to represent his growth in pediatric practice through the years.

In the Forum for March 1894 he pointed out that the weak point of all hospital work for the poor "is due to the faulty conditions in the home." This was a point of view from which he never deviated and represented a conclusion based on hospital social service reports covering a period of four years. In 1890 he established this link between the babies' wards and the home, and he constantly emphasized to the staff that each ill child on the service represented a family tragedy and should be treated as if the parents were at the bedside. His philosophy of social service in the hospital and outside was that society should strive to "atone for its fearful inequalities, not by division and alms, but by strengthening the weak for a more successful effort" and that "the home is the source from which all lasting improvements must come."

In order to make the benefits of the hospital permanent, Dr. Chapin determined in 1902 to try the plan of boarding out in private country homes the bottle-fed infants who were not doing well in institutions or in their own homes. The first station was established in Morristown, N. J. The chance remark of Dr. Chapin that the street along which they were seeking suitable homes for convalescent babies furnished a proper name for the new endeavor resulted in the name "Speedwell Society." Other centers were formed, and by 1940 the society had since its founding taken care of approximately 20,000 children. The object of the Speedwell Society is to place homeless and needy children in the homes of selected and supervised women, who receive a certain sum of money each week plus a bonus for every pound gained by underweight babies. The growth of the project has been constant, both in the number of children cared for and in the broadening of the original

conception of the needs of the community, so that today approximately 1,200 children are received annually.

In 1910 a baby was picked up in a New York city park and a few days later found a temporary home with Dr. and Mrs. Chapin. With care and feeding the boy thrived and grew into an attractive child, who was wanted in a superior home. Out of this incident grew a nursery of four beds on the top floor of their home, into which went unattractive and forlorn waifs. As soon as they had been brought back to good health and promise they were easily placed in permanent homes. Ninety-eight unpromising-looking babies passed through this upstairs nursery in a period of ten years. At the end of that time the home nursery was formally expanded into the Alice Chapin Adoption Nursery. The combined record of these two nurseries is the adoption into homes of nearly 1,700 babies and the finding indirectly of homes for about 2,000 more children. Perhaps the most remarkable journey ever undertaken by a physician and his wife was that of Dr. and Mrs. Chapin in 1917, when they started on a so-called tour of inspection to the Pacific coast and back, stopping practically each night at a different home in which they had placed a child.

Dr. Chapin was primarily a teacher, a missionary and a pioneer. He embodied within himself, both physically and mentally, all that is best in the puritan tradition. He taught a practical kind of pediatrics which was easily grasped by physicians of all grades of preparation. He was perhaps the first to point out that milk is a biologic fluid, and he certainly was the first to establish a breast milk station in the East. He was ten years ahead of the times in recognizing the need of and in establishing a hospital social service that was a practical contribution to the community service of a hospital. The recognition of the importance of placing convalescent children in selected homes in the country is due almost solely to his efforts. He preached from the time when he was beginning the practice of pediatrics that "children give more than they take" and that "they are the great civilizers and humanizers of the race." The core of Dr. Chapin's philosophy of life was undoubtedly summed up in his own words: "The child has done more for the regeneration of the race than all the creeds that have ever been written."

It would not be straying far from the truth if it were to be written that Dr. Chapin in his quiet way was the most significant figure of his generation in the practice and teaching of pediatrics and that he was a pattern after which all doctors who love children would like to mold their lives. His name in the course of time may be easily forgotten (he would have been the first to say that this was proper), but the good which he initiated will go on as long as there are children on earth.

M. C. P.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

BACTERIOSTATIC EFFECT OF PARANITROBENZOIC ACID ON PNEUMOCOCCI IN VITRO. JOSEPH T. KING and AUSTIN F. HENSCHEL, Proc. Soc. Exper. Biol. & Med. **47**:400 (June) 1941.

In vitro experiments disclosed that paranitrobenzoic acid exerts a bacteriostatic effect on type II pneumococci as pronounced as that of sulfathiazole.

HANSEN, Minneapolis.

Vitamins; Avitaminoses

DESTRUCTION OF PROTHROMBIN AND STORAGE OF VITAMIN K. J. GARROTT ALLEN and CORNELIUS VERMEULEN, Arch. Surg. **42**:969 (June) 1941.

Attempting to solve the problem of the rapidity of in vivo destruction of prothrombin and the apparent absence of storage of vitamin K, the authors carefully observed a 37 year old woman with a complete external biliary fistula. Observations on the storage of vitamin K were also made in 3 other cases of biliary fistula. It was concluded that there is rapid in vivo destruction of prothrombin in man. The storage of vitamin K prevents the immediate fall of prothrombin. There is, however, no method of determining how much vitamin K there is in storage. It is therefore essential that preoperative vitamin K and bile salt therapy be carried out in cases of jaundice even though the initial preoperative level of prothrombin is normal, as the body stores may be virtually depleted of the vitamin.

KAISER, Rochester, N. Y.

ASSOCIATION OF NEUROMUSCULAR SYMPTOMS AND CUTANEOUS LESIONS IN VITAMIN A DEFICIENCY: DISCUSSION OF THE ETIOLOGIC RELATIONSHIP. C. N. FRAZIER and S. N. TSAO, Chinese M. J. **59**:309 (May) 1941.

These observers at the Pieping Union Medical College report the case of a 14 year old Chinese boy who had widespread muscular weakness, evidences of a cutaneous rash and a history of vitamin A deficiency. Although the disease resembled a muscular dystrophy, there were some characteristics of polyneuromyelitis. The rash was present over the entire body, in the form of a follicular hyperkeratosis, and disappeared with the use of vitamin A therapy. The therapy, however, did not cure the neuromuscular disease. The disease known as lathyrism has some resemblance to this case, having been produced experimentally by the lack of vitamin A and having a similar effect on the nervous system. It is also suggested that there might be some relationship in this case to a vitamin E deficiency, since myopathic dystrophies much resembling those in man have been produced experimentally.

NEFF, Kansas City, Mo.

RIBOFLAVIN DEFICIENCY AMONG CHINESE: II. CHEILOSIS AND SEBORRHEIC DERMATITIS. H. C. HOU, Chinese M. J. **59**:314 (April) 1941.

Cheilosis is a common feature of pellagra among the children in one of the refugee camps. The author reports on the observations made in these cases and the response to treatment with riboflavin.

The term cheilosis is applied to fissures in each angle of the mouth, with scaly, chapped and reddened lips. The lesion in the corner of the mouth has long been known as perlèche. In pellagrins another sign is common, namely glossitis. In

about half of the 186 children cheilosis was present, usually of mild type. Other children with ariboflavinosis showed ocular lesions only or ocular lesions combined with cheilosis.

Treatment with riboflavin caused improvement in some cases on the third day and healing by the sixth day. Treatment by yeast alone caused a somewhat slower course of healing. The dosage of riboflavin was 15 mg. for the first two days and 10 mg. for the next seven to ten days, followed by 5 mg. daily for a week. The seborrheic dermatitis responded readily to treatment, as did the cheilosis.

NEFF, Kansas City, Mo.

NUTRITIONAL STOMATOGLOSSITIS AMONG THE WAR REFUGEES IN SHANGHAI. P. T. KUO and M. S. HUANG, Chinese M. J. **59**:430 (May) 1941.

This nutritional disturbance had never been reported in China before or during the present war until Kuo and Huang diagnosed it and studied 237 cases. The diet which has been responsible for the present outbreak consists of plain rice or congee with little, if any, protein or other food essentials and therefore produces the usual inflammatory and atrophic gastrointestinal changes from deficiency of the vitamin B complex. Nutritional stomatoglossitis is due to a multiple deficiency of more than one of the many factors of this complex and includes pellagrous stomatitis, which is not the same as the lesions produced by a deficiency of the remaining factors of the vitamin B complex.

The author summarizes 18 instances of the disease, in which the patients were given hospital treatment with proper diet, nicotinic acid, and liver extract; none of these 18 patients were children. The authors believe that pellagrous stomatitis should be treated with nicotinic acid and liver extract and is therefore clinically and therapeutically different from the similar inflammation of the mouth and tongue caused by the deficiency of the other portions of the vitamin B complex.

NEFF, Kansas City, Mo.

Prematurity and Congenital Deformities

A STUDY OF THE RELATIONSHIP BETWEEN FETAL POSITION AND CERTAIN CONGENITAL DEFORMITIES. CHARLES C. CHAPPLE and DOUGLAS T. DAVIDSON, J. Pediat. **18**:483 (April) 1941.

The authors present evidence to explain certain congenital abnormalities as due to uterine pressure and fetal position in utero. In an attempt to determine the cause of extreme lateral bowing of both femurs in a newborn infant, it was discovered that when the infant was placed in a position such that each foot opposed the apex of the lateral curvature of the other thigh, his legs drawn up in tailor fashion so that each leg met the opposite femur at a right angle, the baby enjoyed this position, in fact preferred it to any other. This position was found to account not only for the bowing of the femurs but for the laterally dislocated hips and shallow acetabulums found on roentgen examination. The determination of the "position of comfort" of other newborn babies led frequently to the finding of unsuspected abnormalities. Among these were congenital dislocation of the hips, deviation of the jaw and torticollis. The authors feel that it is important to determine the "position of comfort" as part of a routine examination of all newborn infants, both as a means of anticipation and prevention of abnormalities of the bones and joints and as an aid to the interpretation of existing deformities.

RAUH, Cincinnati.

Acute Contagious Diseases

THE UTILITY OF ALUM-PRECIPITATED TOXOID. KATHERINE H. ANDERSON, Arch. Pediat. **58**:370 (June) 1941.

The literature is reviewed, and the author concludes that alum-precipitated toxoid is a valuable and useful addition to the armamentarium of preventive medicine.

ORR, Buffalo.

EARLY DIAGNOSIS OF POLIOMYELITIS. SIDNEY O. LEVINSON, Illinois M. J. **79**:475 (June) 1941.

Accurate diagnosis of acute anterior poliomyelitis depends on a complete history, a careful examination and a lumbar puncture. BARBOUR, Peoria, Ill.

FACTORS CONCERNED IN THE GROWTH OF CORYNEBACTERIUM DIPHTHERIAE FROM MINUTE INOCULA. SIDNEY COHEN, JOHN C. SNYDER and J. HOWARD MUELLER, J. Bact. **41**:581 (May) 1941.

If a small inoculum of diphtheria bacilli is placed on a culture medium, prompt and rapid growth may not occur. However, growth is stimulated by the addition of serum, milk or commercial preparations of casein. This observation is interesting, and the authors decided to investigate the exact nature of the growth factors. Extensive experiments were carried out, for details of which the original article should be consulted. It was found that oleic acid represents one of the factors concerned in the rapid development of colonies of the Bacillus diphtheriae. The authors were unable to separate the active principle from oleic acid. There is another factor present, and this is now being investigated. It is felt that these phenomena may be of some value in the classification of the diphtheria organism, since the response of the different strains to the growth factors varies considerably.

STOESSER, Minneapolis.

AGE VARIATIONS IN RESISTANCE OF ALBINO RAT TO DIPHTHERIA BACILLI AND TO DIPHTHERIA TOXIN. ERICH SELIGMANN, Proc. Soc. Exper. Biol. & Med. **47**:241 (June) 1941.

Subcutaneous injection of diphtheria toxin into rats of various ages (12 days, 25 days and full grown) revealed that the younger animal was definitely more susceptible to the diphtheric intoxication. On the other hand no differences in the reaction to subcutaneous injections of emulsion of diphtheria bacilli were noted in the various age groups of rats. HANSEN, Minneapolis.

"SUBSTANCE B" OF DIPHTHERIA TOXIN AND DIFFUSING FACTOR. DOUGLAS MCCLEAN, Lancet **11**:595 (May 10) 1941.

No evidence has been obtained of any association between diffusing factor or hyaluronidase and substance B, postulated by O'Meara to be present in toxic diphtheria filtrates.

Only a small proportion of strains of Corynebacterium diphtheriae of any type produce detectable amounts of diffusing factor. Saline extracts of those strains that do produce this enzyme in broth culture show little or no diffusing activity.

The capacity to produce this enzyme is not confined to gravis strains; it can be detected in broth cultures of a few intermediate and mitis strains.

LANGMANN, New York.

AN OUTBREAK OF POLIOMYELITIS: USE OF SULPHAPYRIDINE AND CONVALESCENT SERUM IN TREATMENT. SINCLAIR MILLER and STANLEY WRAY, Lancet **1**:753 (June 14) 1941.

In the early part of the summer of 1940 there was a moderately severe epidemic of poliomyelitis in Harrogate. In four fifths of the 75 cases the patients were children under 15 years of age.

At the outbreak of the epidemic, treatment was largely symptomatic. The earlier results were disquieting; some cases ended fatally, and in others the paralysis extended considerably in spite of treatment. Toward the end of the epidemic, sulfapyridine and serum therapy were given. Results may be summarized as follows:

1. Patients treated symptomatically (18): 1 death; 1 very severely crippled; 4 severely crippled; 6 with slight paralysis; 6 with no paralysis.

2. Patients receiving sulfapyridine in addition to symptomatic treatment (14): 1 death; 3 patients with paralysis that extended considerably while under treatment; 10 with little or no paralysis.

3. Patients receiving both sulfapyridine and convalescent poliomyelitis serum (16, including several of the more seriously ill patients): 3 with no further extension of paralysis; 2 with "excellent recoveries with amazingly little residual paralysis"; 11 with excellent recovery.

"By the use of intravenous therapy a massive concentration of sulphapyridine soluble in the blood and body tissues can readily be attained and to this we attribute the rapid curtailment of infection and of the spread of paralysis. The convalescent serum, we believe, has a dual purpose: it enhances the action of the sulphapyridine and we have little doubt that the serum contains antibodies which help to neutralise the existing toxins and destroy the virus."

LANGMANN, New York.

THE 1937-1938 EPIDEMIC OF POLIOMYELITIS IN NEW SOUTH WALES. KAREN HELMS, M. J. Australia **1**:467 (April 19) 1941.

The epidemic reached its peak earlier in the metropolitan areas than in the rural districts. The height of the epidemic occurred at the time of the highest absolute humidity and temperature. The cases with severest paralysis occurred in the earlier stages of the epidemic. The lower age groups had a greater proportion of patients early and the higher age groups late in the epidemic. A progressive decrease in the percentage of patients in the age group from birth to 4 years is evident during the past twenty years, and it is suggested that better nutrition may be a factor in this.

Poliomyelitis uncomplicated by respiratory paralysis is not an indication for interrupting pregnancy. There is strong evidence to support the view that operations on the nose and throat favor the development of poliomyelitis of the bulbar type.

TENNEY, Madison, Wis.

AN INSTITUTIONAL EXPERIENCE WITH PERTUSSIS VACCINE. E. S. STUCKEY, M. J. Australia **1**:513 (April 26) 1941.

An outbreak of pertussis in an institution housing 38 young children was limited to 10 cases, in 8 of which the disease had developed or was developing at the time of the first injection. Phase I vaccine, in total doses of 37,500,000,000 to 92,500,000,000 organisms, appeared to be effective in the treatment and prophylaxis of the disease.

TENNEY, Madison, Wis.

MENINGOCOCCAL INFECTION WITH SPECIAL REFERENCE TO MENINGOCOCCAL SEPTICAEMIA. S. C. MOSS, M. J.. Australia **1**:548 (May 3) 1941.

Moss emphasizes the importance of the recognition of "meningococcus infection" as separate from meningitis In subacute and chronic forms of meningococcemia the onset is usually sudden, with malaise, shivering, pains in the limbs, especially the legs, and headache. The headache is of varying degrees of intensity and may come and go. This is true also of meningeal signs. Shivering varies from a chilly feeling to a rigor. The pain in the extremities is not necessarily confined to joints, but in the later stages it frequently is; a joint effusion may or may not be present. With the shivering and the rise of temperature there may be a profuse skin action and attendant discomfort, yet the patient may feel quite well with the fall of temperature and have a feeling of comparative well-being. The temperature chart may have a resemblance to that of malaria. As often as not, the temperature is of the common "septic" type. The characteristic rash is most abundantly found on the limbs, but lesions are commonly seen on the back and chest, sometimes on the abdomen and more rarely on the face.

GONCE JR., Madison, Wis.

ACUTE ANTERIOR POLIOMYELITIS AND VITAMIN B DEFICIENCY. K. HELMS, M. J. Australia **1**:717 (June 14) 1941.

Indirect evidence is presented by Helms in support of the hypothesis that hypovitaminosis B_1 is a predisposing cause of poliomyelitis. Poliomyelitis is inclined to occur with greater frequency when the demands for vitamin B_1 are great, as in childhood and pregnancy and after excessive muscular exercise, or when the intake is low, as in poverty. There are points of resemblance between poliomyelitis and beriberi, in that these conditions appear to have similar seasonal incidence, sex incidence and predisposing causes. It has been noted by many observers that muscular exercise contributes to the development of beriberi and of vitamin B_1 deficiency and to the increase of pyruvate in the blood, and there is a growing weight of evidence that muscular exertion is also a predisposing cause of paralytic poliomyelitis. Pregnancy and lactation appear to favor the development of beriberi and of hypovitaminosis B_1. In both poliomyelitis and beriberi the most common and characteristic symptom is flaccid paralysis of the leg muscles; muscle tenderness is characteristic of both diseases. The incidence of poliomyelitis is generally highest in the late summer, at a time when the vitamin B_1 reserve of children must often be at a low level due to an excessive amount of exercise and growth. Of great significance perhaps are: (1) the fact that poliomyelitis did not appear in epidemic form until after 1880, following the introduction of the roller mill process of milling wheat in 1870, and (2) that the greatly increased per capita consumption of refined carbohydrate during the past century has proportionately increased the vitamin B_1 requirement. GONCE JR., Madison, Wis.

STREPTOCOCCAL TYPES IN SCARLET FEVER: THE ASSOCIATION OF CHANGE OF TYPE WITH COMPLICATIONS AND CROSS INFECTION. H. KELSEY and F. V. SCHOLES, M. J. Australia **1**:728 (June 14) 1941.

On the basis of a combined bacteriologic and clinical study the authors conclude that while cross infection as measured by change of type is important and frequent, the complications of convalescence, which are usually ascribed to cross infection, cannot in the main be so explained on the basis of change of type.

GONCE JR., Madison, Wis.

THE USE OF POOLED HUMAN SERUM IN EXPERIMENTAL PERTUSSIS. E. A. NORTH and G. ANDERSON, M. J. Australia **1**:754 (June 21) 1941.

The authors report that pooled normal human serum contains protective antibodies against Haemophilus pertussis infection in mice and suggest that such serum may be of value as a prophylactic in young nonimmunized children exposed to infection.

GONCE JR., Madison, Wis.

Chronic Infectious Diseases

ACETARSONE (STOVARSOL) IN THE TREATMENT OF SYPHILIS IN INFANTS AND CHILDREN. HAROLD A. ROSENBAUM and H. L. FAULKNER, J. Pediat. **18**:750 (June) 1941.

The results of the treatment of 395 syphilitic children with acetarsone over a period of ten years is presented. The dosage used is outlined. Four deaths occurred in this series of patients, and the case histories are summarized. Reactions due to idiosyncrasy to the drug are reported. Reversal of serologic reactions resulted for 232 patients; 22 were transfered from other clinics with reactions already negative; 2 never had positive reactions.

RAUH, Cincinnati.

TUBERCULOUS OBSTRUCTIVE EMPHYSEMA IN CHILDREN: INCIDENCE AND CLINICAL PICTURE; DIAGNOSIS; CASE REPORTS. BERYL BARSBY, Lancet **1**:627 (May 17) 1941.

Tuberculous obstructive emphysema may be a feature of primary tuberculosis in children in cases in which there is emphysema of the lung due to a bronchial narrowing secondary to enlargement of a lymph gland. The bronchial stenosis produced may be partial or valvular, allowing the air to enter the lung at a greater rate than it can leave it.

The author reports 3 cases of his own and reviews 16 published by other observers.

The greatest incidence of the disease occurs between the ages of 6 months and 1 year.

Bronchoscopy has a therapeutic as well as diagnostic value.

LANGMANN, New York.

Diseases of Blood, Heart and Blood Vessels and Spleen

THE EFFECT OF GLUCOSE IN THE PRESERVATION OF CITRATED HUMAN BLOOD STORED AT 4° TO 6° CENTIGRADE. WILLIAM P. BELK and FLORENCE ROSENSTEIN, Am. J. M. Sc. **201**:841 (June) 1941.

A series of observations demonstrate that dextrose (5.4 per cent) prevents the hemolysis of erythrocytes of whole citrated human blood kept at 4 to 6 C. for three to four weeks. With citrate alone hemolysis appears near the end of the first week.

This preserving effect is less marked on the granulocytes, on the platelets and on the clot-forming substances.

One part of isotonic glucose to two parts of blood is effective and has the advantage of not increasing too greatly the amount of fluid to be injected.

It must not be thought that blood preserved by chilling and the addition of dextrose remains in a state of hibernation, or suspended animation. The processes of decay go on steadily, being only retarded by the favorable environment. There is therefore a strict limit to the time that blood for transfusion may properly be stored. This limit is shorter than generally supposed because of the fact that these red blood cells become incapable of substituting for the cells of the recipient prior to suffering any hemolysis.

HENSKE, Omaha.

THE SURVIVAL TIME AFTER TRANSFUSION OF ERYTHROCYTES OF CITRATED HUMAN BLOOD STORED AT 4° TO 6° CENTIGRADE. WILLIAM P. BELK and B. C. BARNES, Am. J. M. Sc. **201**:939 (June) 1941.

Belk and Barnes show by graphic charts that the erythrocytes of citrated human blood kept at 4 to 6 C. survived in recipients as long as the cells of fresh blood when storage time did not exceed two to three days. After this they disappeared with increasing rapidity as storage time increased, until after seven or more days in the "bank" their post-transfusion survival was in no case longer than twenty-four to forty-eight hours.

HENSKE, Omaha.

AN IN VITRO TEST FOR CHEMOTHERAPEUTIC AGENTS USED IN SUBACUTE BACTERIAL ENDOCARDITIS. M. H. UHLEY and L. N. KATZ, J. Infect. Dis. **68**:298 (May-June) 1941

1. An in vitro test is described which offers a suitable preliminary method for determining the effectiveness of the direct antibacterial action of chemotherapeutic agents proposed for subacute bacterial endocarditis.

2. Evidence is presented to demonstrate that fibrin is permeable to sulfonamide derivatives and neoarsphenamine. The drugs are antibacterial in vitro toward Streptococcus viridans within fibrin when used in sufficient concentration.

3. Bacteria in fibrin cultures suspended in serum survive longer than in fibrin, in ascitic medium and even longer than in ascitic medium alone, presumably because of the greater nutrient value of serum and of fibrin.

4. The results suggest that the nutrient value of fibrin and serum are of importance in modifying the ultimate effectiveness of chemotherapy of subacute bacterial endocarditis.

TOOMEY, Cleveland [AUTHORS' SUMMARY].

PROTHROMBIN ESTIMATION USING RUSSELL VIPER VENOM. ROBERT C. PAGE and HOLLIS K. RUSSELL, J. Lab. & Clin. Med. **26**:1366 (May) 1941.

The authors describe their results with a simple modification of Quick's method using Russell viper venom instead of tissue extract. The results compare favorably with those of the Quick (1938) method. The Russell viper venom has the advantage of a constant potency and of clearness, which makes the end point easier to determine.

GARD, Galveston, Texas.

PRIMARY ARTERITIS (PERIARTERITIS NODOSA) AMONG CHILDREN. HADDOW M. KEITH and ARCHIE H. BAGGENSTOSS, J. Pediat. **18**:494 (April) 1941.

Instances of periarteritis nodosa in children as reported in the literature are reviewed, and reports of 2 additional cases are added. The clinical aspects of this symptom complex are summarized and discussed. The most common symptoms and signs are found to be (1) fever, (2) leukocytosis, (3) abdominal and rheumatic pains and (4) evidence of renal disease. In the 2 cases reported the disease processes present were in wholly different stages. In the first case the arteries were the seats of an acute suppurative process. In the second case definitely regressing lesions with proliferative changes were found. The diseases now classified as periarteritis nodosa probably are symptom complexes, or syndromes, referable to a variety of infectious agents.

RAUH, Cincinnati [AUTHORS' SUMMARY].

ANTISTREPTOLYSIN CONTENT OF THE SERA OF NORMAL INFANTS AND CHILDREN. J. E. GORDON and JOHN H. JANNEY, J. Pediat. **18**:587 (May) 1941.

The mean antistreptolysin titer of the blood of normal, healthy children ranging in age from birth to 14 years was determined from studies carried on in Rumania. The mean antistreptolysin titer of serum (from the cord) of newborn infants was found to be higher than that of persons in any other age group. It was greater than the average titer of the mothers of the infants. For individual infants the value was related to that of the mothers, being regularly high for infants with mothers of high titer and low when the mother's titer was low. The high titer of the newborn infant was found to decline sharply to reach a low point at the age of 3 to 6 months. Thereafter a progressive increase was found, so that by the age of 15 years the titer again approximated that at birth.

RAUH, Cincinnati.

EXPERIMENTAL ALIMENTARY AZOTEMIA: COMPARATIVE EFFECTS OF RED CELLS AND PLASMA. C. FRANK CHUNN and HENRY N. HARKINS, Proc. Soc. Exper. Biol. & Med. **47**:7 (May) 1941.

Dogs given red blood cells of beef by means of a stomach tube were found to have an increase in the blood urea nitrogen, whereas none occurred when the animals were given beef plasma. Administration of pure hemoglobin solution to 2 dogs caused a similar rise in the blood urea nitrogen, while iron as iron and ammonium citrates was without effect. The azotemia found in patients with bleeding peptic ulcers probably is explained on the same basis as in the experiments with dogs, namely, that the absorption of the protein fraction of the red blood cells is the source of the increase in blood urea nitrogen.

HANSEN, Minneapolis.

NEUTRALIZATION OF ANGIOTONIN BY NORMAL AND BY ISCHEMIC KIDNEY BLOOD PLASMA. MEYER FRIEDMAN, Proc. Soc. Exper. Biol. & Med. **47**:348 (June) 1941.

In experiments with 6 dogs it was found that normal blood has the power to reduce the physiologic effect of angiotonin, whereas blood from ischemic kidneys does not have this property of preventing an injection of angiotonin from increasing the blood pressure.

HANSEN, Minneapolis.

SUCCESSFUL LIGATION OF PATENT DUCTUS ARTERIOSUS. J. W. GALE, F. J. POHLE and HUNTER ROMAINE, Wisconsin M. J. **40**:296 (April) 1941.

Since August 1938 surgical intervention has been done on 32 patients with patent ductus arteriosus with but 5 deaths, 2 of them of persons who had a superimposed bacterial endarteritis.

The authors add another case, that of a 19 year old girl who had had severe cardiac embarrassment. Her symptoms, which had existed for but six months, were palpitation, dyspnea, tachycardia and precordial discomfort. The operation consisted of ligation of the ductus while respirations were controlled through the use of an endotracheal tube. The characteristic heart sounds promptly became normal except for a soft systolic murmur, limited to the pulmonic area. Three months later she seemed well and had no further difficulty.

JANNEY, Wauwatosa, Wis.

ESTIMATION OF PROTHROMBIN. T. K. OWEN and M. TOOHEY, Lancet **1**:724 (June 7) 1941.

The method of Quick still remains the most suitable, owing to its simplicity. Owen and Toohey's results with normal controls agree with Quick's statements that eleven to fifteen seconds may be taken as normal.

LANGMANN, New York.

Diseases of Nose, Throat and Ear

INFECTIONS OF THE MIDDLE EAR AND NASAL SINUSES. WESLEY C. BOWERS, Bull. New York Acad. Med. **17**:453 (June) 1941.

This article presents in a comprehensive way the problem of infections of the middle ear and nasal sinus. Much misinformation exists, the author states, even among physicians, because of conflicting ideas about the physiology of the nose and its accessory sinuses. The author reviews the anatomy and functions of these structures and their clinical implications. This article must be read in the original to be fully appreciated.

JAHR, Omaha.

THE PROPHYLACTIC USE OF "COLD CAPSULES." A. A. HOLBROOK, Wisconsin M. J. **40**:396 (May) 1941.

Eighty-one students and 7 faculty members of a preparatory school were given "cold capsules" from fall through winter until the end of March. A control group was also observed. Objectively little difference in the incidence of time-wasting colds was found between the capsule-taking group and the control group.

JANNEY, Wauwatosa, Wis.

THE OPERATIVE TREATMENT OF MASTOIDITIS: A REPORT ON WORK DONE AT THE ROYAL NORTH SHORE HOSPITAL OF SYDNEY DURING THE PERIOD JANUARY 1930 TO SEPTEMBER 1940. E. P. BLASHKI and A. L. CLOWES, M. J. Australia **1**:443 (April 12) 1941.

The authors report their observations on the operative treatment of 250 patients with acute and 204 with chronic mastoiditis.

GONCE JR., Madison, Wis.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

PEPTIC ULCER IN CHILDREN. D. M. MOORE, Canad. M. A. J. **44**:462 (May) 1941.

Eight children ranging from 6 to 14 years of age for whom a diagnosis of peptic ulcer had been made are reported on.

Six of the 8 children were underweight. All belonged to families of low income, and most were on relief.

The single feature of the symptomatology was the duration of the abdominal pain. Individually the span was from two and a half months to three years, with a group average of one year. In 7 of the 8 children the pain was localized in the epigastric and paraumbilical region. The pain varied as to relation to food intake, and relief was afforded by the use of soda.

Abdominal tenderness was the most constant physical sign.

Only a presumptive clinical diagnosis of ulcer could be made from the subjective and objective findings.

The diagnosis must depend on the roentgenographic examination.

If a constant and characteristic deformity of the duodenum can be demonstrated by roentgen examination in a child with clinical and laboratory evidence of ulceration, the diagnosis of peptic ulcer is justifiable.

MOORE, Omaha.

CONGENITAL MEGACOLON (HIRSCHSPRUNG'S DISEASE): REPORT OF A CASE TREATED WITH ACETYL-β-METHYLCHOLINE BROMIDE, WITH APPARENT CURE. LOUIS H. BARENBERG, DAVID GREENE and LEON GREENSPAN, J. Pediat. **18**:579 (May) 1941.

A case of congenital megacolon is reported. The child was kept under observation for a period of four and one-half years, during which time the effect of various medical procedures, drugs and surgery were studied. The best results were obtained with the use of mecholyl bromide (acetylbetamethylcholine bromide) given by mouth and liquid petrolatum. At the time of this report the patient was completely relieved of abdominal distention and constipation and his physical development was progressing in a normal manner.

RAUH, Cincinnati [AUTHORS' SUMMARY].

SERUM PROTEIN CONCENTRATION AS A GUIDE TO THE TREATMENT OF DEHYDRATION IN DIARRHEAL DISEASES. EDWARD M. BRIDGE, MAYNARD I. COHEN and T. F. MCNAIR SCOTT, J. Pediat. **18**:709 (June) 1941.

The present study was made on a group of 130 infants under 2 years of age who were admitted to the hospital wards because of problems in fluid regulation. The correlation of day to day changes in the general condition of the infants with corresponding values for serum protein concentration served as the basis of the study. The average normal values of serum protein for premature infants (4.7 per cent), for full term infants up to 3 months (5.7 per cent) and for children 3 months to 2 years (6.5 per cent) offered a basis of comparison with the values for dehydrated infants. In infants who appeared clinically to be severely dehydrated the average serum protein level was 8.3 per cent, in those moderately dehydrated 7.7 per cent and in those slightly dehydrated 6.9 per cent. Examples are cited of infants overtreated and undertreated. Estimation of the serum protein on admission in a case of dehydration and daily serum protein determinations thereafter are a distinct aid in regulating therapy. As the dehydration improves after administration of fluid, the serum protein level falls steadily to normal. When a steady fall in serum protein does not occur in the presence of adequate administration of fluid, subclinical acidosis may be present.

The daily determination of serum protein will prevent overtreatment as well as avoid undertreatment. In the presence of high serum protein levels transfusions are contraindicated, because the addition of more plasma and red blood cells to

a circulation already embarrassed by an excessive concentration of these elements will only increase this embarrassment. Transfusions are indicated for infants with diarrheal diseases whenever anemia, hypoproteinemia or chronic nutritional disturbance is present.

RAUH, Cincinnati.

ASCORBIC ACID ABSORPTION IN INFANTILE DIARRHEA. ARTHUR F. ABT and CHESTER J. FARMER, J. Pediat. **18**:756 (June) 1941.

In a preliminary report it has been noted that ascorbic acid is excreted in small amounts in the stool of the normal infant. Large amounts of orally administered ascorbic acid were excreted in the stool of an infant after catharsis. In the case of 3 infants studied during the course of acute nonspecific diarrhea a considerable increase of the fecal excretion of ascorbic acid is here reported. During the acute diarrhea blood plasma values and urinary excretion tend to remain low, even when large amounts of ascorbic acid have been orally ingested. There is a rapid diminution of fecal excretion of ascorbic acid when the diarrhea abates and the liquid stools change to formed stools. These facts point to a failure of absorption of ascorbic acid from the intestinal tract during infantile diarrhea rather than to an increased destruction of ascorbic acid by bacteria in the intestinal tract. This failure of the absorption of orally administered ascorbic acid during diarrhea in infancy would not be clinically significant in acute diarrhea of short duration. In protracted or chronic diarrhea in infancy the data here presented would indicate the need for parenteral administration of ascorbic acid as a protection against the development of scurvy.

RAUH, Cincinnati [AUTHORS' SUMMARY].

OBSERVATIONS ON THE GASTRIC ACIDITY DURING THE FIRST MONTH OF LIFE. R. A. MILLER, Arch. Dis. Childhood **16**:22 (March) 1941.

Gastric acidity during the first month of life was determined in 50 normal infants. It was found to be high and to show a steady decline from birth to the tenth day. The degree of acidity is highest during the first twenty-four hours, being equivalent to that of a healthy adult. Gastric juice obtained from 63 mature infants and 64 premature infants within eight hours of birth showed higher acidity in heavier infants and achlorhydria in more infants in the lower weight classes. The explanation is given that gastric mucosa is better developed in the heavier infants.

KELLY, Milwaukee.

PROGNOSIS AND TREATMENT OF ACUTE DIFFUSE PERITONITIS IN CHILDREN SINCE THE ADVENT OF CHEMOTHERAPEUTIC DRUGS. KENNETH M. ALFORD, Arch. Dis. Childhood **16**:43 (March) 1941.

From the survey on appendical peritonitis it is felt that the mortality rate has been appreciably cut down by the use of the chemotherapeutic drugs, just as it was in cases of primary peritonitis. There is no question that the best method of treatment of such peritonitis is to diagnose the acute appendicitis before rupture. However, children's hospitals will continue to have neglected cases in which the parents have not called in a physician until after perforation, in which there has been indiscriminate use of laxatives and cathartics for the treatment of abdominal pain and in which a diagnosis of acute appendicitis has been missed. Chemotherapy, although it will not take the place of any of the surgical measures previously mentioned, has proved to be another weapon in the armamentarium against appendical peritonitis as well as a specific for primary streptococcic and pneumococcic peritonitis.

KELLY, Milwaukee.

PROGNOSIS OF CONGENITAL PYLORIC STENOSIS TREATED WITH EUMYDRIN [ATROPINE METHYLNITRATE]: CASES CURED MEDICALLY; OPERATIONS; DEATHS. RICHARD. H. DOBBS, Lancet **1**:661 (May 24) 1941.

A series of 40 patients with congenital hypertrophic pyloric stenosis were treated with atropine methylnitrate; if response was unsatisfactory within ten days,

the patient was operated on. The 13 infants who responded rapidly to the treatment with atropine methylnitrate were almost exclusively those who were 4 weeks old or over when vomiting began and who had increased in weight since birth. They were discharged within ten days. The second group (10 patients) showed some response within ten days and were discharged within three weeks of admission. In the third group were 4 patients who were discharged after thirty days; the prolonged stay of 3 of these was due to causes other than persistance of vomiting.

In the fourth group were 12 infants who had not responded within ten days and were operated on.

In all, 27 of the 40 children were cured by medical treatment and 8 by operation; 1 patient died during medical treatment and 4 after surgical treatment.

At present gastroenteritis is the greatest menace to the infants with pyloric stenosis admitted to English hospitals.

"And though it is true that skilled surgeons operating on large numbers of hypertrophic pyloruses can get good results, yet the effects of surgical intervention continue to appear as a cause of fatalities in the reported cases and are certainly responsible for an appreciable percentage of the deaths from pyloric stenosis."

LANGMANN, New York.

SULFATHIAZOLE IN THE TREATMENT OF DYSENTERIC ENTEROCOLITIS. F. J. MENCHACA, L. M. CENTENO and N. ALBARRACIN, Arch. argent. de pediat. **15**:432 (May) 1941.

The authors report their experience in treatment of the dysenteric forms of enterocolitis with sulfathiazole. They feel that in general the drug has a favorable action and is effective in improving this condition. The daily dose employed generally was 0.02 Gm. or less.

Few of the patients showed any toxic symptoms. The drug was generally well tolerated.

SCHLUTZ, Chicago.

Nervous Diseases

THE ETIOLOGY OF SYDENHAM'S CHOREA: ELECTROENCEPHALOGRAPHIC STUDIES. SAUL J. USHER and HERBERT H. JASPER, Canad. M. A. J. **44**:365 (April) 1941.

In this study 23 patients with chorea were studied for a period of over eighteen months. In addition, 7 patients with questionable chorea were examined, and also a patient with active rheumatic carditis and no chorea. Electroencephalograms from 48 children of comparable ages were used as controls. In all cases of severe chorea pronounced generalized abnormalities were observed in the electroencephalogram.

Three patients with mild chorea showed only slight abnormalities.

Clinical improvement showed a definite correlation with decreased abnormality in the encephalogram.

The abnormal electroencephalogram of chorea is not specific for this condition, since it resembles closely certain dysrhythmias found in the electroencephalograms of epileptic patients between attacks and those found in association with acute head injury and with other conditions causing general impairment of cerebral function.

MOORE, Omaha.

STAPHYLOCOCCAL MENINGITIS TREATED WITH SODIUM SULFATHIAZOLE. THOMAS J. DONOVAN, J. Pediat. **18**:518 (April) 1941.

A case of Staphylococcus aureus meningitis in a 7 month old boy is reported, with recovery following oral and intravenous administration of large doses of sulfathiazole and its sodium salt. A high level of sulfathiazole (9.5 mg. per hundred cubic centimeters) was obtained in the spinal fluid by the use of intra-

venous injections of sodium sulfathiazole. However, this level fell off rapidly, more so when the intravenous administration was discontinued. The relative freedom from toxic reactions, especially in the blood, after 101.85 Gm. of the drug had been given over a period of thirty-two days is noted. The suggestion is made that repeated intravenous doses at intervals of six to eight hours should be the best method of obtaining therapeutic concentrations of the drug in the spinal fluid. Oral administration alone is a poor method of adequate treatment of staphylococcic meningitis with this drug.

RAUH, Cincinnati [AUTHOR'S SUMMARY].

A METHOD FOR DETERMINING LOSS OF PAIN SENSATION. FRED E. D'AMOUR and DONN L. SMITH, J. Pharmacol. & Exper. Therap. **72**:74 (May) 1941.

Loss of pain sensation was determined by the reaction to heat from a Mazda lamp focused on the tip of a rat's tail for a controlled time period; movement of the rat's tail indicated perception of pain. More than 10,000 experiments were made on several hundred rats. The results showed very little variation in the reactions, while those of other reported methods have shown such wide variation as to make results at times seem questionable. The effectiveness of the members of the opiate group (dilaudid, diacetylmorphine, morphine, codeine and pantopon, in the order given) was that stated in several pharmacology texts. Sodium amytal and several venoms showed no analgesic properties. The authors note that while the pain resulting from burning does not parallel exactly the pain of many clinical conditions, such as may occur in carcinoma, the method has the great advantage of giving uniform results in testing the analgesic value of new and clinically untried drugs.

PILCHER, Cleveland.

INTERNAL HYDROCEPHALUS DUE TO SYRINGOMYELIALIKE PROCESS OF AQUEDUCT OF SYLVIUS. VINTON D. SNEEDEN and CHARLES P. LARSON, Northwest. Med. **40**:44 (Feb.) 1941.

A case of occlusion of the aqueduct of Sylvius is presented, producing internal hydrocephalus due to a process thought to be identical with that of syringomyelia. The patient, a white boy of 3½ years, had been normal until he was 2 years and 8 months, when symptoms developed suggesting an infection of the upper respiratory tract. A high temperature and rigidity of the neck were present. He was discharged from the hospital in five days improved. After this he remained in bed with a low grade fever and was unable to walk alone when allowed to get up. His extremities became somewhat spastic. There was an undetermined degree of bilateral choked disk. The first encephalogram showed no penetration of air beyond the aqueduct of Sylvius. Taking of another encephalogram, a week later, was followed by respiratory difficulty and death. The pathologic changes noted were limited to the brain. There was no evidence of inflammatory change. Lesions present in the aqueduct of Sylvius were similar to those observed in syringomyelia elsewhere in the central nervous system.

ROBERTSON, Omaha.

REVIEW OF PNEUMOCOCCIC MENINGITIS. HARRY D. PASS, Northwest Med. **40**:210 (June) 1941.

Pneumococcic meningitis is of not too infrequent occurrence. It is most common in the winter months. Usually it is secondary to pneumonia, otitis media, fracture of the skull, sinusitis or mastoidectomy. The diagnosis rests on the characteristic signs of meningeal irritation and on the results of an examination of the spinal fluid. Specific antipneumococcus serum and sulfapyridine are two specific weapons. Early high levels of sulfapyridine in the blood and in the spinal fluid are desirable. The author reports 2 fatal cases in which the spinal fluid showed only a trace of sulfapyridine although blood levels were high.

ROBERTSON, Omaha.

BLOOD PANTOTHENIC ACID VALUES IN MULTIPLE SCLEROSIS. LOUIS SIEGEL, TRACY J. PUTNAM and JOHN G. LYNN, Proc. Soc. Exper. Biol. & Med. **47**:362 (June) 1941.

This study was undertaken because of the fact that the nerve lesions of animals suffering from pantothenic acid deficiency have a superficial resemblance to the lesions of multiple sclerosis. The pantothenic acid content of the blood from 6 patients with advanced multiple sclerosis was the same as that of 6 control subjects; it thus appears that this disease is not due to a deficiency of pantothenic acid.

HANSEN, Minneapolis.

EPILOIA. L. M. QUILL and E. C. MARTING, Surgery **9**:581 (April) 1941.

Quill and Marting describe the syndrome of epiloia observed in 7 persons of three generations. Although the mother of the first and seventh patients (the grandmother of the other 5 patients) was not examined clinically, the history of epileptic seizures, adenoma sebaceum and tumors of the nail bed makes the diagnosis of epiloia a valid presumption. If this is granted, the study reveals direct passage of the disease through three generations. The study discloses that if the patient with epiloia lives through puberty and is capable of mating transmission of the disease is possible. The reason for so few examples of transmission lies in the fact that the average affected patient is so mentally and physically incapacitated at puberty that marriage and mating do not occur. Study of the family tree discloses that 1 daughter (case 1) of the patient with the original case of epiloia transmitted the disease in all its intensity to all 4 of her children who lived to puberty, whereas the other daughter (case 7) with signs of the disease apparently did not pass it on to her 2 older children. There is no evidence of the disease in the other 2 children of the patients with the original case of epiloia. Neither was the condition found in their children. This suggests that the disease is not recessive, but rather is incompletely dominant. The tumors of the nail bed, usually an uncommon accompaniment, are of particular interest because of their presence in all 7 cases. The presumption here is that epiloia is transmitted, even in its minute details. The direct transmission of the disease from parent to offspring through three generations proves that the syndrome is hereditary, i. e., genotypical, as suggested by Fabing.

J. A. M. A.

INTRAMEDULLARY EPIDERMOID CYST OF SPINAL CORD. MURRAY A. FALCONER and REGINALD S. HOOPER, Brit. J. Surg. **28**:538 (April) 1941.

The authors point out that epidermoid and dermoid cysts occurring within the substance of the spinal cord are uncommon. Nine examples were found in the literature. The authors' case is that of a 32 year old man in whom a stiffness of left knee with a limp developed. Iodized poppyseed oil injected into the spinal column showed a filling defect opposite the third thoracic vertebra. The condition was completely relieved by operation. The authors recommend lumbar puncture, Queckenstedt's test and injection of iodized poppyseed oil in patients showing symptoms referable to the spinal cord.

KEITH, Toronto, Canada.

FOUR CASES OF MENINGITIS CURED WITH SULFAPYRIDINE. F. BAZÁN, R. MAGGI and E. SCHTEINGART, Arch. argent. de pediat. **15**:203 (March) 1941.

The authors report 4 cases of pneumococcic meningitis; the ages ranged from 2½ to 7 years. Sulfapyridine was used in initial massive doses and continued throughout the treatment in doses sufficient to maintain an adequate concentration of the drug in the blood and spinal fluid.

The effects of the treatment were spectacular. The patients regularly showed marked improvement. Within forty-eight hours the temperature dropped to normal

and all meningeal symptoms declined. All of the patients made a complete and uneventful recovery without showing any residuals.

Three of the patients received the drug by oral route, and to a fourth it was given by the intraspinal route for the first three days. SCHLUTZ, Chicago.

REPORT OF A CASE OF GENERALIZED TREMOR. A. GAREISO and F. ESCARDO, Arch. argent. de pediat. **15**:231 (March) 1941.

The authors report this unusual condition in a child 23 months of age. The disorder followed a moderate attack of grip. It lasted about a month and a half and manifested itself as a general tremor of both the head and the extremities. There was marked hypotonia, and sleep was much disturbed. There was no fever, and a careful clinical examination revealed no manifest pathologic changes. The spinal fluid was normal. The condition was apparently a postinfectional encephalitic process, probably of a virus type. SCHLUTZ, Chicago.

THE GUILLAIN-BARRÉ SYNDROME AND POLIOMYELITIS. H. WISSLER, Kinderärztl. Praxis **12**:69 (March) 1941.

A typical Guillain-Barré syndrome in a boy 9 years old is described. Important points to be kept in mind in differentiating this condition from poliomyelitis are:

1. The speed with which paresis develops is slower in radiculoneuritis than in poliomyelitis.

2. In radiculoneuritis the paresis is often generalized and symmetric and rarely reaches the stage of complete paralysis. In poliomyelitis paresis often is not symmetric or generalized, with the exception of the preparalytic stage, and complete paralysis is frequently found.

3. Pain and tenderness are more predominant in radiculoneuritis than in poliomyelitis.

4. "Albuminocytologic dissociation" may occur in later stages of poliomyelitis, but rarely does one find even then that the albumin content of the spinal fluid is as high in poliomyelitis as in radiculoneuritis.

Correct diagnosis is important because of prognosis. Patients with radiculoneuritis recover completely though slowly. HEYMANN, Cleveland.

DILANTIN SODIUM THERAPY IN EPILEPSY: A REVIEW OF LITERATURE AND A PRELIMINARY REPORT OF SIX CASES. FENG YING-K'UN and HSU YING-K'UEI, Chinese M. J. **59**:508 (June) 1941.

The authors recommend the dosage for adults and children above the age of 6 years as 0.1 Gm. three times daily, always given orally; for children under 3 years of age the dosage at the beginning of treatment should be 0.03 Gm. two to four times daily. The dilantin sodium is mixed with cream to disguise the bitterness.

In the 6 cases reported in this communication, all the patients were adults or adolescents, the latter being 2 boys, 13 and 15 years old respectively. The effect seemed to be favorable and equal to that produced by bromides or phenobarbital. Hypertrophy of the gums was seen in 2 cases. The authors present this as a preliminary report, since the period of observation had been only about nine months. They regard the drug as an alternative for patients who are refractory to other drugs. NEFF, Kansas City, Mo.

EPIDEMIC ENCEPHALITIS IN CHILDREN. T. KISHINAMI, Acta pædiat. japon. **47**: 339 (March) 1941.

According to Kishinami, a total of 183 cases of epidemic encephalitis in children were observed in the Pediatric Clinic of the Tokyo Imperial University during the years 1919 to 1939. The youngest patient was an infant 6 months old. The

peak of the epidemic occurred each year from the middle of August to the beginning of September. The initial symptoms of the disease were fever, vomiting, headache, colic and sensory disturbances. Conjugated deviation, ptosis and sluggish light reflex were noted in many patients. The patellar tendon reflex was for the most part accelerated. Examination of cerebrospinal fluid disclosed a slight elevation of pressure, the fluid usually water clear in appearance but giving a strongly positive globulin reaction, together with a moderate increase in sugar content and some degree of pleocytosis during the early stage of the disease. In general, the blood picture was that of leukocytosis with a relative increase in eosinophils during the first stages. The mortality rate was 10.3 per cent in 183 cases. Familial and cross infection in the hospital was never encountered.

KATO, Chicago.

Diseases of the Genitourinary Tract

NEPHRITIS IN CHILDREN. JOSEPH K. CALVIN, Illinois M. J. **79**:464 (June) 1941.

Calvin gives a review of acute glomerular nephritis and lipoid nephrosis in children, too comprehensive for abstracting.

BARBOUR, Peoria, Ill.

SERUM PROTEIN REGENERATION FOLLOWING USE OF AMINO ACIDS IN NEPHRITIS (NEPHROTIC STAGE). WILLIAM J. MESSINGER, Proc. Soc. Exper. Biol. & Med. **47**:281 (June) 1941.

Two adult subjects with chronic nephritis in the nephrotic stage (albuminuria, elevated blood cholesterol and edema) who had been under observation for several years were given intravenous injections of amino acids. The first subject was given 500 cc. of a 5 per cent solution of amino acid obtained by enzymatic hydrolysis of casein with 5 per cent dextrose daily for twenty-four days, with no effect whatever on the level of the serum proteins. The second subject was given 180 cc. of a 20 per cent solution diluted with equal parts of distilled water daily for fourteen days. A small but definite rise in the serum protein, chiefly in the albumin fraction, occurred in this subject. Four months later this patient was given 300 cc. of a 15 per cent solution of the amino acid daily for sixteen days, at the end of which time the serum albumin had risen from 2.4 to 3.4 Gm. per hundred cubic centimeters. Both subjects consumed diets containing 120 Gm. of protein with low fat content. No untoward reactions occurred in these subjects.

HANSEN, Minneapolis.

CONCENTRATIONS OF SULFATHIAZOLE AT WHICH BACTERICIDAL ACTION IS LOST FOR BACTERIA COMMONLY PRESENT IN URINARY INFECTIONS. H. F. HELMHOLZ and NORA LARSON, Proc. Staff Meet., Mayo Clin. **16**:404 (June 25) 1941.

A concentration of 10 mg. of sulfathiazole per hundred cubic centimeters of urine inhibits the growth of most strains of bacteria, except Streptococcus faecalis and Pseudomonas aeruginosa.

By prophylactic administration of 2 to 3 grains (0.12 to 0.2 Gm.) of sulfathiazole five times a day bacterial infections associated with postoperative catherization should be avoided.

MILLER, South Bend, Ind.

THE UNDESCENDED TESTICLE: AGE INCIDENCE; DESCENT IN RELATION TO PUBERTY; POSSIBLE INDICATIONS OF FUTURE DESCENT; RISKS OF LEAVING THE TESTICLE UNDESCENDED; ROLE OF SURGERY AND ENDOCRINOLOGY. R. E. SMITH, Lancet **1**:745 (June 14) 1941.

Observations were made since 1931 on boys attending two schools: one with approximately 600 boys from 13 to 18 years of age, and the other with 400 boys aged from 9 to 18 years. It was possible to follow the progress of most of 50 cases for periods varying from 2 to 9 years.

Eleven boys out of a group of 511 between the ages of 12 and 15 years had undescended testicles, an incidence of 2.2 per cent. Spontaneous descent occurred in 7.

From his study the author concludes that undescended testicles associated with clinical hernia should be treated surgically; others should be given the chance to descend spontaneously at puberty. If they fail to do so, operation should be performed without delay. A preliminary course of endocrine therapy will not often cause descent but will make operation easier. Most of the testicles which do not descend spontaneously will be found to be ectopic or to have anatomic obstructions.

The aberrant testicle is supposed to be particularly liable to inflammation, trauma, torsion and malignant disease. In his ten years as school medical officer, Smith has encountered 7 cases of torsion of the spermatic cord, 2 of hydatid of Morgagni, 1 of sarcoma of the testicle, 2 of large hydroceles, and 2 of hemorrhage from the pampiniform plexus, probably traumatic.

Atrophy does not take place until after puberty. Transplantation into the scrotum does not necessarily remove the danger of a malignant condition developing in the testicle.

LANGMANN, New York.

Diseases of the Ductless Glands; Endocrinology

NEONATAL CORTICAL INSUFFICIENCY (ADDISON'S DISEASE) ASSOCIATED WITH THE ADRENOGENITAL SYNDROME. H. E. THELANDER and MOLLIE CHOLFFIN, J. Pediat. **18**:779 (June) 1941.

The case of a boy exhibiting symptoms of a syndrome represented by adrenal cortical insufficiency associated with the adrenogenital syndrome is presented; the child's progress during the first fourteen months of life is described, and the methods of treatment used are outlined. A discussion of the symptoms, laboratory findings, pathology, etiology, treatment and prognosis of this symptom complex is included in the report.

RAUH, Cincinnati.

INFLUENCE OF OESTROGENS ON EXPERIMENTAL CANINE DIABETES MELLITUS. F. G. YOUNG, Lancet **1**:600 (May 10) 1941.

The administration of large doses of pure estrogen (estrone, estriol and diethylstilbestrol) to 4 dogs with pituitary diabetes, and to 1 depancreatized dog was found to exert no obvious antidiabetic action. In fact, with estrone and estriol the effect was prodiabetic rather than antidiabetic.

The author discusses the reasons for the differences between these results and those of investigators who have successfully treated with estrogens both experimental pancreatic diabetes in the dog and postmenopausal diabetes mellitus in women.

LANGMANN, New York.

THE EFFECT OF OESTROGENIC SUBSTANCES ON THE KIDNEY OF TRICHOSURUS VULPECULA. A. BOLLIGER and A. J. CANNY, M. J. Australia **1**:697 (June 7) 1941.

Renal damage was produced in Trichosurus vulpecula, the common Australian phalanger or opossum, shortly after the injection of estrogens (estradiol benzoate, estradiol dipropionate and diethylstilbestrol). The urea content of the blood began to rise soon after the injection of a fairly large dose, and in the experiments which terminated fatally severe retention of urea was noted. The histologic changes observed in the kidneys consisted of cloudy swelling and necrosis of the tubular epithelium and calcification of the necrotic epithelium similar to that seen in mercury bichloride poisoning. Calcification was also occasionally seen in the muscular coat of arcuate and interlobar blood vessels.

GONCE JR., Madison, Wis.

VITAMIN B_1 AND DIABETES. DEMETRIO SODI and ERNESTO SODI, Prensa méd. mex. **6**:73 (June 15) 1941.

In pigeons with polyneuritis, there is found a large amount of pyruvic acid, in the form of pyruvate in the brain, in the blood and in the cardiac muscle. It is known that in polyneuritis cellular respiration is diminished and pyruvic acid is increased. Thiamine increases respiration and diminishes or destroys pyruvic acid. A diet rich in carbohydrates produces signs of avitaminosis B_1 more rapidly than a diet rich in fats. Pigeons subjected to a diet lacking vitamin B_1 showed polyneuritis after four days if the diet was rich in carbohydrates and after seven days if it was rich in fat.

It appears that the frequency of avitaminosis B_1 in diabetes is associated with lack of vitamin A.

The therapeutic action of vitamin B_1 extends from day to day, although it is always in second place, since first place is taken by insulin.

GIFFEN, Toledo, Ohio.

Diseases of the Muscles, Bones, Joints and Lymph Glands

SKULL FRACTURES IN CHILDREN AND THEIR SEQUELAE: A CRITICAL ANALYSIS OF 285 CASES. MEYER S. FOX and SAMUEL S. BLANKSTEIN, J. Pediat. **18**:629 (May) 1941.

A study of 285 patients with fracture of the skull admitted to the Milwaukee Children's Hospital between 1922 and 1939 is reported. The study was made to determine the frequency and severity of the immediate symptoms following fractures of the skull in children and to find out how these children fared in later life. There were 15 deaths, a mortality rate of 5.26 per cent. The importance of shock is seen from the fact that it was present in 14 cases and resulted in 7 deaths within forty-eight hours after injury. Unconsciousness was present in 46.6 per cent of the cases, and the duration appeared to be directly related to the degree of intracranial damage. Headaches and dizziness were seldom present. The frequent occurrence of bleeding from the ears, spontaneous nystagmus and ecchymosis of the eyelids suggests the importance of early and thorough otologic and ophthalmologic examinations. Sequelae resulting from the head injury, although not as common as those in adults, are sufficiently frequent to warrant consideration because of their possible effect on the development of the child. An important factor in preventing sequelae and complications appears to be proper management of the child at the time of injury. An adequate period of rest in bed, combined with conservative measures of treatment, have given the most favorable results.

RAUH, Cincinnati.

VITAMIN THERAPY IN PROGRESSIVE MUSCULAR DYSTROPHY: VITAMIN B_6, OTHER FACTORS OF THE B COMPLEX AND VITAMIN E. ANGUS MCBRYDE and LENOX D. BAKER, J. Pediat. **18**:727 (June) 1941.

Six patients with typical progressive pseudohypertrophic muscular dystrophy were treated with vitamins B and E. No improvement occurred in 2 patients who received wheat germ oil by mouth for two months and in 1 patient who received alpha tocopherol intramuscularly on alternate days for thirty-six days. Four patients received pyridoxine hydrochloride (vitamin B_6) orally, 100 mg. daily, for periods of twenty-one to thirty-six days. Since oral administration of this compound resulted in no improvement and since bi-weekly injections were ineffective in 2 patients, 4 patients were given the drug intravenously in daily doses of 50 mg. for twenty to thirty days, but the result was the same. Then a combination of thiamine hydrochloride, riboflavin, nicotinic acid and pyridoxine hydrochloride was tried. This was administered to 4 patients for thirty days. The only improvement during the entire course of therapy was a gain in weight in 1

patient and an improvement in the sense of well-being in the others. This was attributed to the general effect of the vitamin therapy, since the patients' diets had been deficient in some of the vitamins used. RAUH, Cincinnati.

ABSORPTION OF DRUGS THROUGH THE BONE MARROW. DAVID I. MACHT, Proc. Soc. Exper. Biol. & Med. **47**:299 (June) 1941.

Intramedullary injections of various drugs were made in dogs, cats, rabbits, guinea pigs, rats and mice, which revealed that aqueous solutions as well as volatile oils of drugs are rapidly absorbed, whereas fixed oils are absorbed more slowly. Epinephrine base in oil, introduced by intramedullary injections, produces a pronounced and long-sustained rise in blood pressure, much longer than that obtained by intramuscular injection. HANSEN, Minneapolis.

CLEIDOCRANIAL DYSOSTOSIS. MANUEL LOPEZ PONDAL, An. Soc. puericult. Buenos Aires **7**:66 (April-June) 1941

Two cases are presented This disease is hereditary and congenital; it is characterized by aplasia, total or partial, of the clavicle; by broadening of the head; by open linear sutures, and by persistence and enlargement of the anterior fontanel as well as of the longitudinal suture and the bilateral eminences.

According to Gaston Levy, there have been reported but 50 cases in the world. GIFFEN, Toledo, Ohio.

Diseases of the Eye

RHINOSPORIDIUM SEEBERI INFECTION IN THE EYE. NORMA B. ELLES, Arch. Ophth. **25**:969 (June) 1941.

This is a very extensive review of a rare fungous disease due to Rhinosporidium seeberi which occurs in animals and man with a wide geographic distribution. Three cases of the ocular condition have been discovered in the United States, 1 by the author. WESCOTT, Chicago.

BILATERAL GLAUCOMA ASSOCIATED WITH UNILATERAL NAEVUS FLAMMEUS. LEON H. EHRLICH, Arch. Ophth. **25**:1002 (June) 1941.

Instances of glaucoma in association with naevus flammeus have been noted, but only in possibly 3 cases has the nevus been unilateral and the glaucoma bilateral. WESCOTT, Chicago.

CROSS-EYED CHILDREN. BRITTAIN FORD PAYNE, Arch. Pediat. **58**:365 (June) 1941.

Cross-eye often may be cured if the condition is recognized early and the proper treatment prescribed. The advice of a trained ophthalmologist should be considered and followed. The cooperation of parents and the general physician is needed and the confidence and enthusiasm of the affected child should be developed. If the child is within the school age, he should have the cooperation of the teacher; but above all there must be a willingness on the part of the child and of his guardians to cooperate completely if anything is to be accomplished. ORR, Buffalo.

Skin Diseases; Allergy

SCARLATINOID ERYTHEMA OF UNKNOWN ETIOLOGY. ARCHIBALD L. HOYNE and LAWRENCE R. LEVITON, Arch. Pediat. **58**:69 (Feb.) 1941.

The authors report a symptom complex in which a scarlatinoid eruption was present. The persons in this group were in intimate contact with each other, and the condition appeared to be contagious, though a common etiologic factor

could not be discovered. Throat cultures on blood agar and blanching tests for scarlet fever all gave negative results. All patients had fever leukocytosis and pharyngitis. A profuse nasal discharge was present in all the infants. There is no mention of desquamation.

ORR, Buffalo.

STUDY ON REAGIN CONTENT OF SPINAL FLUID. MCKINLEY LONDON, J. Allergy **12**:244 (March) 1941.

The author was unable to demonstrate reagins in the spinal fluid of atopic persons even though they were present in high concentrations in the blood.

HOYER, Cincinnati.

CUTANEOUS AND SYSTEMIC REACTIONS OBSERVED DURING ORAL POISON IVY THERAPY. BEDFORD SHELMIRE, J. Allergy **12**:252 (March) 1941.

This excellent piece of work records the reactions to oral administration of ivy oleoresin diluted in corn oil. A child's nurse employed in the home of the author was the subject of the experiments, which extended over a period of many months. A reduction of sensitivity of the skin was obtained.

The article is too long to abstract in detail, but it is very interesting and well worth reading from the standpoint of the extent to which the nurse cooperated even though she must have been uncomfortable at times from her reactions.

HOYER, Cincinnati.

HISTAMINASE IN ALLERGY: A STUDY OF ITS EFFECTS ON SKIN REACTIVITY TO HISTAMINE AND TO ALLERGENS. HYMAN MILLER, ROLAND C. HAWES and GEORGE PINESS, J. Allergy **12**:335 (May) 1941.

Through the use of the wheal and the flare of the intradermal test as a typical allergic phenomenon for fairly exact control and measurement, the present investigation attempted to demonstrate an in vivo activity of histaminase which might furnish an experimental basis for its clinical use in the prevention and alleviation of allergic symptoms.

Oral and parenteral administration of histaminase preparations did not significantly influence cutaneous reactions to histamine or the sensitivity of passively sensitized sites to a fish allergen. HOYER, Cincinnati [AUTHORS' SUMMARY].

ALLERGY IN RELATION TO PURPURA. J. WARRICK THOMAS and J. R. FORSYTHE, J. Lab. & Clin. Med. **26**:1105 (April) 1941

Ten cases of purpura haemorrhagica were studied from the viewpoint of allergies involved. A family history of allergy was obtained for 8 patients. All these patients had some allergic manifestations. Two of this group with frank allergic manifestations showed no improvement in their purpuric symptoms until after splenectomy.

GARD, Galveston, Texas.

FAVISM, A SINGULAR DISEASE CHIEFLY AFFECTING THE RED BLOOD CELLS. ALDO LUISADA, Medicine **20**:229 (May) 1941.

The author describes the distribution and clinical and laboratory aspects of this disease. It occurs chiefly on the island of Sardinia, but cases have occurred in continental Europe, and a few cases have been reported in the United States. It is due to inhalation of the pollen of the fava (or faba) bean or to ingestion of the seeds of this plant. The disease is characterized by sudden or gradual onset of weakness, dizziness, nausea, vomiting, pallor and chills and fever. Later hemoglobinuria and icterus appear, and the liver and spleen become enlarged. The symptoms last from two to six days. In fatal attacks, which are usually limited to children, death usually occurs within the first two days, rarely on the third. The blood shows anemia and leukocytosis, with evidence of regeneration.

The author presents citations from the literature and records of his own original research to support his theory that the syndrome is due to an allergy, or sensitization mechanism. Sensitization frequently occurs in infancy, and freedom from attacks may develop spontaneously in later life.

In treatment intramuscular injection and transfusion of blood, intramuscular injection of epinephrine hydrochloride and intravenous injection of calcium gluconate have been used, and iron has been given after attacks. Specific desensitization is being tried by Manai, but results are not available. Avoidance of contact with fava proteins is advised.

LIMPER, Louisville, Ky.

EFFECT OF DIET ON ANAPHYLAXIS IN THE WHITE RAT. JULIA T. WELD and LUCY C. MITCHELL, Proc. Soc. Exper. Biol. & Med. **47**:168 (May) 1941.

Contradictory results in the production of anaphylaxis in rats suggested that the diet of the animals played a role in the phenomenon. Rats sensitized with either horse or sheep serum could not be thrown into anaphylactic shock until they were at least 10 weeks of age. Addition of yeast, vitamin A, casein or calcium carbonate and potassium dihydrogen phosphate (KH_2PO_4) to the basic bread diet did not alter appreciably the anaphylactic response in the animals. However, rats poorly nourished to the point of losing weight could not be sensitized to anaphylactic shock.

HANSEN, Minneapolis.

IMPETIGO CONTAGIOSA: THE STREPTOCOCCIC AND STAPHYLOCOCCIC VARIETIES AND THEIR TREATMENT AND MANAGEMENT. STEPHAN EPSTEIN, Wisconsin M. J. **40**:383 (May) 1941.

Impetigo contagiosa caused by the streptococcus can in typical cases be easily differentiated clinically from that caused by the staphylococcus. (Koch's requirements for proof of causation have been fulfilled for both types.) The first is characterized by superficial lesions covered with thick yellowish crusts, honey-like in color. It starts as a red spot with a transitory blister on top, which quickly crusts and later, owing to admixture of blood, may have a dirty brownish color. Swollen regional glands are frequent. It is superficial and rarely leaves scars. Favorite locations are the face, neck, hands and scalp. On the fingers it differs in that there are rapidly developing bullae which form "whitlows" about the nails. It may be primary or secondary and occasionally is complicated by nephritis, rarely by erysipelas.

Staphylococcic impetigo is usually characterized by bullae, the fluid contents of which are clear. These bullae may become flattened, and they usually persist several days. After rupture the lesions become covered with a crust which is thin, flat and varnish-like, of a gray or brown color, quite different from the thick streptococcic crusts. In infants they usually occur in the folds, burst more rapidly and may erode large parts of the integument.

Another form of staphylococcic impetigo is that with circular kidney-shaped lesions consisting of flat blisters and crusts around healing centers. It resembles ringworm.

The staphylococcic impetigo is almost always primary. Complicating nephritis is rare. Occasionally furuncles occur. Streptococcic impetigo is chiefly a disease of childhood; staphylococcic impetigo, of all ages from infancy through adult life. The two types occur with about equal frequency. Treatment of the different types and stages of impetigo is discussed in detail and a list of prescriptions given. Sulfanilamide and its derivatives used locally and internally as indicated are very valuable. The use of silver nitrate and of ultraviolet rays and many other forms of treatment are discussed. Pemphigus neonatorum is best handled by the "dry" treatment. Control of the extension and transmission of impetigo received consideration.

JANNEY, Wauwatosa, Wis.

EFFECTS OF SOLAR RADIATION ON THE SKIN IN CHILDREN AT THE SEASHORE. G. FRONTALI, Riv. di clin. pediat. **39**:20 (Jan.) 1941.

This essay covers the general subject of solar radiation in children and was given before the International Society of Hydrology and Climatology.

HIGGINS, Boston.

THE USE OF MAGNESIUM SULFATE ASSOCIATED WITH EPHEDRINE IN THE TREATMENT OF INFANTILE ASTHMA. A. V. FREYRE, Arch. argent. de pediat. **15**:165 (Feb.) 1941.

The author advises the use of magnesium sulfate in combination with ephedrine in the treatment of infantile asthma. The preparation is given intramuscularly in the following combination: ephedrine chloride, 0.015 Gm.; magnesium sulfate, 0.75 Gm.; distilled water, 3 cc., and procaine hydrochloride, 0.01 Gm. This treatment can be repeated three to four times within twenty-four hours. It must not be used if the disease is complicated by cystitis, nephritis or meningitis. The author has treated a total of 9 patients with good results. In no case were there any harmful effects.

SCHLUTZ, Chicago.

ULCERS OF THE LEG: ECTHYMA. GEORGE MILLAN GUTIERREZ, Prensa méd. mex. **6**:11 (Jan. 15) 1941.

Ecthyma starts as an impetigo, a lesion of the epidermis which through lack of care and neglect in poorly nourished infants becomes deep and reaches the dermis, producing an ulceration most frequently on the legs. The cause is the streptococcus, the same organism which causes the common impetigo. Ecthyma is inoculable and autoinoculable, and similar ulcerations or pustular lesions are found surrounding the primary lesion. The differential diagnosis is discussed.

The following treatment is recommended:

1. Elevate the leg.

2. Remove the crusts by the use of hot moist fomentations, as the lesions must be free of crusts before treatment can be effective.

3. Apply fomentations of resorcinol or of alcohol:

Resorcinol ..... 1. Gm.
Mix and pulverize; place in no. 3 papers.
Directions: Dissolve 1 paper in 1 liter of boiled water.

or

Copper sulfate..... 1.0 Gm.
Zinc sulfate..... 1.0 Gm.
Distilled water..... 500.0 cc.

Allow fomentations to remain on for one-fourth to one-half hour.

4. Touch the ulcer with 1 per cent solution of silver nitrate.

5. Apply mild mercurial ointment U. S. P. or the following ointment:

Subcarbonate of iron..... 1.0 Gm.
Petrolatum ..... 30.0 Gm.

6. If the ulcer is slow in healing, it must be stimulated, for instance by use of the following ointment:

Silver nitrate..... 0.25 Gm.
Peruvian balsam..... 5.0 cc.
Zinc oxide..... 5.0 Gm.
Petrolatum ..... 50.0 Gm.

GIFFEN, Toledo, Ohio.

Brief Etiopathogenic Consideration of Edema in Children. Efrain Nava Uriza, Rev. mex. de pediat. **11**:44 (Jan.) 1941.

If one considers the mechanism of edema as a watery increase of the interstitial system, the intracapillary hydrostatic pressure and the colloidal-osmotic pressure of the proteins lead to the displacement of the water contained in the plasma and the tissues. As the osmotic pressure of the proteins is decreased, owing to a lowering of plasma albumin, the water passes from the plasma to the tissues. During the last war prolonged inanition without proteins caused edema of variable intensity. In early childhood needs are 3 to 4 Gm. daily of protein per kilogram of body weight; it is usually given in the form of milk and, in the poorer classes, broths of corn and rice. In this age period edema occurs most frequently.

Two case histories are given. One child, 18 months old, arrived in the arms of the mother and was prostrated. The child had passed round worms and was edematous. A soy bean food and treatment for ascaris infection were given, with recovery. Another child, 16 months old, had diarrhea, vomiting and fever. It had received only rice gruel and when treated with soy bean gruel quickly improved.

Giffen, Toledo, Ohio.

Surgery and Orthopedics

The Effect of Local Application of Sulfanilamide upon Wound Healing. Max Taffel and Samuel C. Harvey, Proc. Soc. Exper. Biol. & Med. **47**:202 (June) 1941.

Study of the healing of wounds by determination of the tensile strength revealed that local injection of a suspension of sulfanilamide crystals did not retard the healing of wounds in the stomach of rats. Only occasionally did the histologic picture reveal the presence of a foreign body reaction.

Hansen, Minneapolis.

The Treatment of Burns. Arthur A. Schaefer, Wisconsin M. J. **40**:391 (May) 1941.

Burns are the third most common cause (8 per cent) of all fatal accidents. In children from birth to 4 years they cause 22 per cent of all fatal accidents, and in those between 5 and 14 years of age, 11 per cent of all fatal accidents. Oil or grease should not be applied as emergency treatment, and less attention should be paid to the local lesion and more to the patient himself in preventing pain and shock. Warmth, fluids (usually administered intravenously) and chlorides must be supplied plentifully the first few days. Large amounts of plasma are lost, and administration of human serum or plasma may be most important. The local treatments with cleansing agents and tannic acid solution are described.

Janney, Wauwatosa, Wis.

Bow Leg. Walter P. Blount, Wisconsin M. J. **40**:484 (June) 1941.

Bow leg, formerly mostly rachitic, is a diagnostic problem. The newborn child normally has considerable bowing of both femurs and tibias, associated with rotational variations from the adult form. As this gradually corrects itself, knock knees appear, which persist until the child is from 4 to 6 years of age. The partially flexed position of the knee in the infant gradually straightens and changes to a backknee (genu recurvatum) in the second and third years. Early radical correction of these conditions should not be attempted, since correction usually occurs spontaneously.

On rare occasions a condition called tibia vara occurs, in which at about 1 year of age the bow legs, instead of improving, become worse owing to an angulation of the tibia at the proximal epiphysis associated with beaklike medial projection of the metaphysis. This often requires surgical correction, but the operation

should be deferred until the progress of the deformity has stopped. The condition may be unilateral or bilateral and is related to the other manifestations of osteochondrosis. Occasionally it does not develop until late in childhood and may be associated with trauma, as is the bow leg due to known injury of the tibial epiphysis. Fracture through the distal epiphysial line, causing premature arrest of its growth, may also cause bowing. Rachitic bowing is ordinarily recognized in connection with other rachitic signs. Dietetic control, including provision of the necessary vitamins, usually corrects the condition, and operation is rarely needed except in neglected cases.

A congenital form of bowing rarely seen may occur in the lower third of one tibia only. There is increased density of the shaft with rather abrupt angulation. Osteoclasis or osteotomy is disastrous in this condition because union rarely occurs, even with bone grafts. Dysplasia, chondro, fragilitas ossium, bone cysts and tumors are occasional attendant complications.

JANNEY, Wauwatosa, Wis.

THE ROLE OF LATEROVENTRAL POSITION IN THE DRAINAGE OF ABSCESSES OF THE ILIAC FOSSA. PAULO DE SAO TIAGO, Rev. méd. munic. **1**:373 (March) 1941.

Four cases are presented, with the following recommendations: The same gauze packs used the first day are sufficient to keep the wound open; these packs are removed as soon as possible without producing hemorrhage, and the rubber drains are removed in forty-eight hours. This treatment shortens the time in bed.

SANFORD, Chicago.

Teeth and Dentistry

THE PEDIATRIC ASPECT OF DENTAL CONDITIONS IN CHILDHOOD. ARTHUR F. ABT, Arch. Pediat. **58**:210 (April) 1941.

The author discusses some of the factors that may influence adversely the normal development of the teeth in children. In his conclusion he states that there are still great gaps in the knowledge of teeth and their pathologic state and that the problem is far from solved.

ORR, Buffalo.

STUDIES ON DENTAL CARIES: XI. SEX DIFFERENCES IN THE CARIES SUSCEPTIBILITY OF THE VARIOUS MORPHOLOGICAL TYPES OF PERMANENT TEETH. HENRY KLEIN and CARROLL E. PALMER, Child Development **12**:207 (June) 1941.

In order to compare the susceptibility to caries of each type of permanent tooth in boys and girls, the numbers of teeth of particular type which have been attacked by caries (decayed, missing and filled) per hundred boys and per hundred girls are related to the duration of time after eruption that these teeth have been exposed in the mouth of the children of each sex. This procedure, carried out with data collected on more than 6,000 elementary and high school children, fails to reveal a consistent difference between the sexes in the susceptibility to caries of the individual types of permanent teeth. On the whole, the observations indicate that sex per se is not an important variable influencing susceptibility to caries of the individual types of teeth in Hagerstown, Md., school children of the chronologic ages 6 through 19 years.

PALMER, Washington, D. C.

THE ACTION OF FLUORINE IN LIMITING DENTAL CARIES. J. F. VOLKER and B. G. BIBBY, Medicine **20**:211 (May) 1941.

The authors review the studies that have been made to show that drinking water having a high content of fluorine causes a decrease in dental caries, whether or not the enamel is mottled. Various experiments are quoted to support

the several theories of the mechanism of the action of fluorine in limiting caries. The authors believe that fluorine from the saliva or drinking water combines with the enamel of the teeth to form an enamel which is peculiarly resistant to destruction by organic acids or by bacterial action.

The authors suggest that the application of strong solutions of a fluoride to the teeth as a part of dental prophylaxis or the use of weaker solutions as dentifrices or mouth washes may prove practical means of controlling caries.

LIMPER, Louisville, Ky.

Miscellaneous

CYSTIC HYGROMA IN INFANCY: REPORT OF THREE CASES INCLUDING ONE WITH CONGENITAL LIPOMA. ABRAHAM TOW, Arch. Pediat. **58**:73 (Feb.) 1941.

Three cases are reported in which there was surgical intervention, with recovery.

ORR, Buffalo.

THE PEOPLE'S MISERY: MOTHER OF DISEASES: AN ADDRESS, DELIVERED IN 1790 BY JOHANN PETER FRANK, translated from the Latin with an introduction by HENRY E. SIGERIST, Bull. Hist. Med. **9**:81 (Jan.) 1941.

Johann Peter Frank, best known through his epoch-making work, "System einer vollständigen medicinischen Polizey," was no doubt one of the most outstanding figures in the great public health movement that took place in the second half of the eighteenth century. In 1785 he accepted the chair of clinical medicine at the University of Pavia, and a year later he became Protophysicus and Director General of Public Health of the Austrian Lombardy and the Duchy of Mantua. This gave the organizer in Public Health an excellent chance to use his abilities. He broke with the custom of eulogizing the candidates at the graduation exercises and read instead addresses on clinical subjects. In the early part of 1790 the enlightened Emperor Joseph II died, and the hopes for social reforms seemed doomed. It was at this time that Frank chose not a clinical subject but the one presented here and gave the address with his usual candor and fearlessness.

Starting with the lack of prenatal care and the overworking of the pregnant woman, he enlarged on the poor start of the newborn child. He was aware of the increase of abortions and premature births in districts where the women had to work up to the time of the confinement. Even cows and horses got better care, because premature delivery meant a loss to the owner. If the mother and child were able to survive the confinement, new troubles arose. The worn-out mother was unable to nurse. The description of the starving child suckling in vain is most pathetic. In some cases, in which the mother had sufficient milk, poverty forced her to take on the infant of wealthy parents and wean her own child; the latter could not digest the improper artificial food and wasted away. If she, however, surreptitiously put her own child to her breast, she might contaminate it with "the poison that she has already transmitted to her husband," or she would be exhausted in a short time. The artificial feeding, a pap consisting of milk and wheat flour (as used in Germany) or a coarser one made of water and corn flour (as used in Italy), undigestible for such young infants, caused innumerable ailments, such as "flatulence, tension of the abdomen, colic, copious development of worms, insuperable obstruction of the mesenteric glands, atrophy, rickets, hydrops, convulsions, finally even death."

The people were so poor and lived in such misery that, like the cattle among whom they lived, they knew nothing of the principles of humanity and of course nothing of how to protect their offspring. This explains why even a light epidemic caused a regular slaughter every year.

He discussed the detrimental effects of child labor on the health of children and adolescents. Premature labor caused "lack of slenderness, symmetry and natural perfection" as well as of "grace, strength and natural excellence."

"Let the government expel from our provinces *the people's misery, most powerful mother of diseases.*"

(It is most important that such documents, which hardly any one nowadays is able to read or would take the time to translate, are presented in a translation which does the original full justice.)

ROSENTHAL, St. Paul.

FURTHER STUDIES ON THE EFFECT OF MASSIVE INTRAVENOUS INFUSION IN NARCOTIC POISONING. THEODORE KOPPANYI and REGINALD A. CUTTING, J. Lab. & Clin. Med. **26**:1140 (April) 1941.

On the basis of their work with animals the authors recommend massive injection of fluids in treatment of certain narcotic poisonings. They have used to date barbiturates, chloral hydrate, bromide and others. They do not believe this treatment should replace rapidly acting analeptics, but think it should be used as an adjuvant.

GARD, Galveston, Texas.

PHARMACOLOGICAL STUDIES IN EXPERIMENTAL ALCOHOLISM: I. THE EFFECT OF SYMPATHOMIMETIC SUBSTANCES ON THE BLOOD-ALCOHOL LEVEL IN MAN. MAX RINKEL and ABRAHAM MYERSON, J. Pharmacol. & Exper. Therap. **71**:75 (Jan.) 1941.

Certain publications indicate that amphetamine sulfate favorably affects the recovery from acute and chronic alcoholism. These statements led the authors to investigate whether the results were not due to a lowering of the blood alcohol level in these subjects. The effects of amphetamine sulfate, paredrine hydrobromide (p-hydroxy-α-methylphenethylamine hydrobromide), epinephrine hydrochloride and atropine sulfate were studied in psychiatric hospital patients who had been known to the authors for several years. After control studies of the blood alcohol level after oral, intravenous and intraduodenal administration of ethyl alcohol, the level was again determined at frequent intervals for two hours some days later with the simultaneous administration of the drugs. It was found that each of the drugs lowered the blood alcohol level, amphetamine being the most active, followed in order by paredrine, epinephrine and atropine. The cause of the lowered level was decreased absorption from the intestine and delayed gastric emptying time, not increased secretion, oxidation or diffusion.

PILCHER, Cleveland.

COOLING DRUGS AND COOLING CENTRES. F. E. ROSENTHAL, J. Pharmacol. & Exper. Therap. **71**:305 (April) 1941.

There is experimental evidence in the literature of the presence of a "cooling" center in the diencephalon. The author found that very small doses (one thousandth of the minimal effective subcutaneous dose) of picrotoxin and aconitine injected into the diencephalon of rabbits resulted in a fall of temperature of several degrees (C.) in from one to four hours. The two drugs act synergistically. The cooling effect of picrotoxin is suppressed by phenobarbital and paraldehyde, but picrotoxin annuls simultaneously the fall of temperature produced by these drugs. In other kinds of experimental fall of temperature (calcium sleep, aconitine) picrotoxin shows an additive or even potentiated cooling effect. These results support those of others that there is a temperature-lowering, or "cooling" center in animals.

PILCHER, Cleveland.

INHIBITION OF SULFAPYRIDINE BY THE PROCAINE IN CHEST FLUIDS AFTER PROCAINE ANESTHESIA. DANIEL A. BOROFF, ANITA COOPER and JESSE G. M. BULLOWA, Proc. Soc. Exper. Biol. & Med. **47**:182 (May) 1941.

Pleural fluid aspirated from 10 tuberculous patients under anesthesia induced with procaine hydrochloride (about 1.5 cc. of 2 per cent solution) was found to

have an average concentration of 0.0002 per cent procaine. Procaine (which is known to be a compound related to paraaminobenzoic acid and therefore to have antisulfanilamide action) in the concentration of 0.0002 per cent exhibited antisulfapyridine action to the pneumococcus type III in vitro in concentrations of sulfapyridine as high as 0.005 per cent. Thus the procaine concentration after aspiration with this anesthetic may be sufficient to allow bacterial growth temporarily by inhibiting the action of sulfapyridine in vitro. Ethyl carbamate (urethane) in concentrations as high as 0.05 per cent did not inhibit the action of sulfapyridine in vitro.

HANSEN, Minneapolis.

THE NATURE OF DISEASE IN INFANCY. J. C. SPENCE, Lancet **1**:777 (June 21) 1941.

This is an abstract of the Bradshaw lecture delivered before the Royal College of Physicians, March 7, 1940. It discusses the following broad categories: (1) inborn errors of structural development; (2) inborn errors of metabolism; (3) mechanical injuries; (4) temporary failure to establish the mechanisms of independent existence; (5) deficiencies of diet; (6) neuromuscular disorders of organ function; (7) infections.

LANGMANN, New York.

THE WHITE HOUSE CONFERENCE ON CHILDREN IN A DEMOCRACY. KATHARINE F. LENROOT, Bol. Inst. internac. am. de protec. a la infancia **14**:370 (Jan.) 1941.

A summary of the personnel, views and recommendations of the White House Conference of 1939 is presented. It is emphasized that the social gains of the past in maternity and child health problems, housing and prevention of exploitation of child labor should be continued, that special safeguards to assure equitable treatment of children in minority groups should be set up and that a plan should be developed for care of children in migrant families. The broad objective for the nation should be to provide every needed facility for health protection and for educational and vocational guidance. "Youth with special aptitudes should be afforded opportunity for their full development as their contribution to the strength of the Nation. Opportunity for continued education or useful employment should be assured to all young people, not merely to those engaged in preparedness programs."

LESLIE, Evanston, Ill.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

JAMES H. WALLACE, M.D., *President, in the Chair*

Clinical Meeting, April 21, 1942

Congenital Pulmonary Cyst. DR. ARTHUR ROSENBLUM.

This boy, aged 14 months, was first seen at the age of 5 weeks. He did not appear ill, had a good color, was well developed and well nourished and had no feeding difficulties. The unusual condition was slightly labored respirations. Breath tones were suppressed over the entire right side of the chest, almost absent in the right axilla and loud over the left side of the chest. The apex impulse was displaced to the left. The percussion note was hyperresonant over the right side of the chest.

Roentgen examination showed that a large multilocular air cyst occupied most of the right side of the chest, displacing the heart to the left and compressing some normal lung at the right apex. The cyst extended partly into the left side of the chest. In the differential diagnosis the possibility of pneumothorax or obstructive emphysema also had to be considered. The characteristic roentgenogram of course was conclusive.

The cyst is undoubtedly congenital in origin. It is believed that this type of cyst originally contains fluid, ruptures into a bronchus, expels its contents and becomes an air cyst. If the communication to the bronchus is small, a valve action may occur and the cyst may expand. The chief danger is that it may become progressively expansile. There is also danger of infection, with abscess formation.

In most of the reported cases in which the cyst was interfered with there have been fatal results. It would be theoretically possible to cure the condition either by obliterating or by enlarging the communication between the cyst and the bronchus. This has been attempted in various cases, usually unsuccessfully. A cure has been reported by injection of iodized poppyseed oil into the cyst, with resulting sclerosis of the communication. As long as the child has remained perfectly well, however, it is felt best to do nothing at present, as his chance of surviving a surgical procedure will be better at a later age.

Chronic Urinary Retention Due to Congenital Hypertrophy of the Interureteric Ridge. DR. HARRY ROLNICK.

This 6 year old boy had been a constant bed wetter and was also incontinent during the day. His condition had been diagnosed as enuresis until he was seen at Mandel Clinic in December 1941, when it was noted that his bladder was noticeably overdistended, with more than 400 cc. of residual urine. His chronic urinary retention simulated that seen in an old man with prostatic obstruction suffering from chronic retention and overflow or paradoxic incontinence.

Intravenous urograms showed only fair function of the right kidney, with a rather pronounced hydronephrosis and hydroureter. The left kidney had practically no function; there was faint evidence of secretion on a roentgenogram after three hours.

Cystoscopy revealed unusual prominence of the interureteric ridge. The fundus of the bladder was visualized only with difficulty, and it had the appearance of a large diverticulum. Retrograde pyelograms showed severe hydronephrosis and

hydroureter of the left side, with practically no function, and a lesser degree of hydronephrosis of the right side, with only fair function on that side.

Suprapubic cystotomy was performed on Jan. 3, 1942, and the greatly hypertrophied interureteric ridge, extending between the two ureteral orifices, was completely resected by means of electrocautery. The bladder, when opened, had the appearance of an hourglass bladder, the greatly hypertrophied ureteric ridge acting as a bar between the trigone and the fundus. This hypertrophied interureteric ridge acted also as a diaphragm against the neck of the bladder, blocking the internal vesical orifice and thus preventing urinary outflow from the bladder. When the level of the urine in the fundus of the bladder rose above the level of this ridge, it could then pass into the trigone and out through the urethra. At the end of the operation the fundus of the bladder was level with the neck of the bladder, and there was no further obstruction to the urinary outflow. This was also noted later on cystoscopy when the bladder had closed. The postoperative course was stormy, but the suprapubic wound closed after three and a half weeks, and sulfadiazine (2-[paraaminobenzenesulfonamido]-pyridine) controlled the infection.

The patient has had good urinary control since that time, and the so-called enuresis has ceased. Repeated intravenous and retrograde pyelograms have shown pronounced improvement in renal function, with complete return to normal of the hydronephrotic right kidney and striking improvement of the previously functionless left kidney. He presents the typical picture of improvement following relief of long-standing obstruction of the neck of the bladder, and in him the improvement has been much more dramatic than that seen in the aged patients.

Two Recoveries from Influenzal Meningitis. Dr. Willard Kerman.

The first child, a boy 11 months old, weighing 30 pounds (13.6 Kg.), was admitted to Sarah Morris Hospital on the fifth day of illness following a convulsion. There were no signs of meningeal irritation. Sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) had been administered prior to admission, and this, together with sulfadiazine and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) given in the hospital, totaled 70 Gm. in twenty-one days. He also received 75 mg. of anti-influenza rabbit serum (Alexander).

The second boy, aged 11, weighing 75 pounds (34 Kg.), was admitted on the third day of illness, complaining of chills, fever and stiff neck. The blood and spinal fluid cultures yielded organisms on the first and third hospital days. He was given a total of 95 Gm. of sulfapyridine and sulfathiazole in sixteen days and 75 mg. of serum. Only two lumbar punctures were made.

Congenital Atresia of the Duodenum in a Premature Infant: Operation with Recovery. Dr. Joseph K. Calvin.

This premature infant weighed 4 pounds 10 ounces (2,097.8 Gm.) at birth. Vomiting began on the first day of life. It was slight at first, later becoming more profuse and forceful, but never actually projectile; it usually occurred soon after feeding. The vomitus did not contain bile but did occasionally show blood, although the prothrombin time was normal; there was no fecal odor to the vomitus.

The stools were meconium at first; later none were passed. No test was made for cornified epithelial cells in the stool. Abdominal distention, not pronounced at first, became gradually more noticeable, although never as great as one would expect from the roentgenogram.

Inasmuch as small premature infants frequently vomit a good deal and have large, distended abdomens, treatment at first was directed toward maintaining fluid balance, by blood transfusions and other means. When the symptoms progressed further, roentgen studies were made. The infant had lost one third of its body weight. The roentgenogram, a flat plate of the abdomen (scout film), was absolutely diagnostic. No contrast medium was given, because of the great

danger of aspiration by vomiting. The film showed an enormously dilated stomach and portion of the duodenum, which appeared to occupy the entire abdomen. No air or gas bubbles were seen in the rest of the bowel.

At operation a greatly dilated stomach and duodenum proximal to the ampulla of Vater was found. A fibrous band about 1 inch (2.5 cm.) long connected this with the rest of the intestines, the loops of which were completely collapsed and smaller in circumference than a lead pencil. A posterior gastroenterostomy was done. Drop ether anesthesia was used.

Preoperative and postoperative treatment consisted of parenteral administration of fluids, blood serum, whole blood, oxygen, sulfathiazole and vitamin K. Feedings by mouth were withheld for some time postoperatively, because the edema about the gastrojejunostomy opening in itself produced a temporary continuance of the obstruction, as did the small lumen of the distal portion of the intestine until air passed in to distend it. After an expected stormy postoperative course, the infant surprisingly recovered.

The case is presented because (1) duodenal atresia proximal to the ampulla of Vater is very unusual; (2) successful treatment of duodenal atresia is rare; (3) this infant lost one third of its birth weight of 4 pounds 10 ounces (2,097.8 Gm.) and still survived; (4) the flat plate of the abdomen without a contrast medium was absolutely diagnostic, and (5) all newborn infants with intestinal obstruction should be given the chance of survival by surgical intervention.

Anorexia Due to Depression. Dr. Maxwell Gitelson.

This girl, aged 4 years, suffered from anorexia and vomiting of four months' duration. She weighed only 23 pounds (10.4 Kg.), and a high intestinal obstruction was suspected. When this diagnosis could not be confirmed, psychiatric consultation was requested. It was found that the child was reacting severely to a series of disappointments: first, weaning from the breast at the age of 4 months, when another pregnancy intervened; second, the birth of this next sibling and its claim to the mother's entire attention; third, the return home of the father, who had been imprisoned, and his intrusion into the relation which had finally been established between the patient and the mother, and, finally, the birth of a second younger sibling.

The child had failed to respond to medical treatment and was critically ill when psychotherapy was started. At the end of seven months of daily treatment with the technics of the "play interview," the child was well. She has remained well after a year and a half, despite the birth of a third sibling.

The material elicited during treatment revealed that her rage toward the rivals who intervened between her and her mother took the form of fantasies which involved their destruction orally. The function of eating thus became connected with bad tendencies which were rejected. The vomiting appeared as an anxiety reaction which served as a defense against the tendency to exercise the stigmatized function of eating. The patient rejected food together with the dangerous fantasies of destroying her rivals by chewing them up.

The syndrome is considered a depression, and it is a nucleus of the adult type of depression.

Neuroblastoma Sympatheticum: Report of Two Cases. Dr. Philip Rosenblum.

The first patient, a 6 month old girl, was first examined at the age of 3 months. She had not been examined since leaving the hospital, and the mother had noticed nothing abnormal. The infant weighed 15½ pounds (7 Kg.) and was of good color and happy.

On examination a large mass was discovered in the abdomen, having the configuration of the liver and extending well below the umbilicus. Intravenous

pyelography, roentgen examination of the bones and metabolic studies did not disclose any abnormalities. On exploratory laparotomy a very large, diffusely infiltrated liver was observed. No primary tumor was found. Biopsy showed the growth to be a neuroblastoma sympatheticum, and roentgen therapy was instituted by the tumor clinic. The liver, which had reached almost to Poupart's ligament, is now just midway between the costal arch and the umbilicus. The child has been gaining weight and is happy, and there is no evidence of further spread of the tumor.

The second baby, aged 5 months, was admitted to the hospital because of pneumonia. On examination a nodular mass the size of a small walnut was found in the left cervical region. The skin over the mass was freely movable. Reactions to tuberculin tests were negative. A roentgenogram showed an area of calcification in the mass. The bones were normal on roentgen examination.

A "punch" biopsy revealed the mass to be a neuroblastoma sympatheticum, which has responded to roentgen therapy.

Neuroblastoma was originally thought to be extremely malignant; it is now known that it may sometimes undergo spontaneous maturation into ganglioneuroma. It may also regress spontaneously from hemorrhage or necrosis; it responds to roentgen therapy properly administered. Faber reported 25 per cent of the patients in a series of 40 cases alive three to eight years after diagnosis of this condition.

Epidural Abscess. DR. IRWIN RUBELL.

B. W., a Negro girl aged 7 years, was admitted to the Sarah Morris Hospital on Dec. 26, 1941, with the following history: Ten days prior to admission she became ill, with elevation of temperature, toxemia and weakness of both legs. There was some stiffness of the back and neck. A spinal puncture four days after the onset of the illness revealed 750 cells per cubic millimeter, of which 92 per cent were polymorphonuclear leukocytes. The reaction to the Pandy test was 3 plus; the total protein content was 70 mg., and the smear and culture showed Staphylococcus aureus. A diagnosis of staphylococcic meningitis was made, and therapy with sulfathiazole was instituted. In spite of heroic doses of sulfathiazole over a period of several days the condition became progressively worse; local tenderness over the lumbosacral region increased, and a flaccid paralysis of the lower extremities developed. A perinephritic abscess was suspected.

When neurosurgical consultation was obtained, an epidural abscess was tentatively diagnosed. A needle was introduced into this area, and pus was obtained from the epidural space. An immediate laminectomy was performed. After a stormy course of several weeks, the child recovered and gradually regained nearly complete function of the lower extremities.

The point to be emphasized in this case is the ease with which a mistaken diagnosis of meningitis may be made, with the twofold danger of carrying infection from the epidural space into the spinal canal during lumbar puncture and producing meningitis and of delaying the performance of a laminectomy, without which recovery is impossible. The possibility of an epidural abscess must be considered when meningeal symptoms are accompanied by extreme tenderness localized over a definite portion of the spine. The needle should be introduced very cautiously, so that pus is obtained before the dura is punctured.

The prognosis as to life is grave, and recovery without laminectomy is unknown. With operation, the mortality rate is 50 per cent. Prognosis as to function depends on whether the spine or the roots are involved; lesions in the spinal cord are irreversible, and the paralysis is permanent. The roots may heal, with return of function. The recovery of this patient, in spite of the delayed laminectomy, is probably due to the large doses of sulfathiazole. The return of function is probably due to localization of the infection below the level of the cord, with only the cauda equina involved.

Intracerebral and Extradural Abscess of the Brain: The Effect of Therapy with Sulfanilamide or One of Its Derivatives on Diagnosis. DR. L. M. WEINBERGER.

The following report of a case illustrates the diagnostic difficulties encountered in diagnosing intracranial infection while the patient is receiving therapy with sulfanilamide or one of its derivatives.

The patient, a girl aged 13, was admitted to Sarah Morris Hospital on Feb. 2, 1942. Two weeks prior to admission she contracted a sore throat. This was followed in a few days by a feeling of stuffiness in the head and bouts of severe burning and pressing headaches in the supraorbital region, worse at night and aggravated by changes in position. There was a daily rise of temperature to 102 to 103 F.

On examination, the child did not appear ill. There were a reddened pharynx, a purulent postnasal discharge and rather pronounced tenderness over the frontal sinuses. A diagnosis of acute frontal sinusitis was made, and sulfadiazine therapy was started, 15 grains (0.97 Gm.) being administered every six hours. Twenty-four hours after admission, a generalized convulsion occurred suddenly. Thorough neurologic examination showed no evidence of meningeal irritation or focal signs. Lumbar puncture showed 132 cells, 50 per cent of which were polymorphonuclears; the pressure was 200 mm. of water. During the next five days she remained comfortable except for intermittent attacks of mild headache. Repeated neurologic examinations failed to disclose evidence of neurologic involvement or of meningeal inflammation. The temperature ranged between normal and 102 F. Four additional lumbar punctures showed spinal fluid cell counts between 140 and 180, but the percentage of lymphocytes approached 100 per cent; there was no significant increase in intraspinal pressure. Although no clinical evidence of involvement of the central nervous system appeared, the presence of a pleocytosis of the spinal fluid, the occurrence of the convulsion, the persistence of mild intermittent headache and the continued mild fever led to the conclusion that an intracranial extension of infection had occurred. An extradural abscess was thought to be the probable lesion.

On February 12, with the patient under anesthesia induced with avertin with amylene hydrate, an exploratory operation through the left frontal bone about an inch (2.5 cm.) above the frontal sinus disclosed an intracerebral abscess containing 5 cc. of free pus, lying about 2 cm. beneath the surface of the cortex, and an extradural abscess containing 6 to 8 cc. of free pus. There were rough purulent granulations on the dura. An area of bone was removed in order to allow the intracerebral abscess to gravitate to the surface. Two days later the abscess was tapped through the previous incision, and a few more cubic centimeters of pus was obtained.

The postoperative course was entirely uneventful; the temperature was normal at the end of a week, and the patient was discharged after three weeks. The wound was closed by secondary suture eight days after drainage of the abscess. Administration of sulfadiazine was continued for a week after operation. The organism was Staphylococcus aureus haemolyticus.

In view of this and similar experiences it is apparent that the customary clinical picture of cerebral abscess will seldom if ever be seen when sulfanilamide or one of its derivatives is used. Though diagnosis is more difficult, the surgical results are immeasurably better. As time goes on, clinicians will appreciate that the intracranial infections of patients treated with these drugs are less severe; therefore the indications for surgical intervention will necessarily have to be revised.

Osteoid Osteoma. DR. S. A. WILE.

This patient, a white boy aged 14, entered the hospital because of a painful tender swelling on the anterior surface of the right leg, which had slowly increased in size during the past year; there was dull intermittent pain in this area in recent months. There was no history of previous trauma or of fever.

On examination, there was a hard mass on the anterior middle surface of the right tibia. This area was moderately tender to pressure. There was no increased heat or redness. The temperature, blood count and sedimentation rate were normal.

A roentgenogram of the right leg showed a spindle-shaped area of thickening along the anterior medial cortex of the tibia. This involved mainly the cortex and was densely sclerotic. At about the center of the deformity was a small area of faint radiolucency.

The entire tumor area was removed at operation. The resected block of bony tissue cut with difficulty; in one place there was a small elevated roughened nodule. Microscopically, this nidus was found to be composed of osteoid and atypical bone. The mass of osteoid was sharply delimited from the overlying cortex, which was thickened. There was no evidence of hemorrhage or inflammatory reaction.

The clinical diagnosis of osteoid osteoma may be suspected in an adolescent or young adult if there is complaint of well localized pain of some months' duration with little local swelling and no local heat. There is no elevation of temperature or increase in the leukocyte count. The x-ray picture will usually conform with one of the stages in development of the osteoid osteoma. All patients are apparently completely cured by surgical removal of the tumor.

Aleukemic Lymphatic Leukemia. DR. A. MATHESON.

This 6 year old Italian child was admitted to the hospital because of periods of fever, lassitude and loss of weight in the preceding three months. The only noteworthy abnormalities found were a moderately enlarged liver, leukopenia, lymphocytosis and atypical lymphoid cells in material obtained from sternal puncture. She was in the hospital for seven months; further study did not give any additional information. Sepsis finally developed, following extraction of a tooth at home, and the child died.

The unusual feature in this case was the failure of circulating blood to show the true nature of the disease until shortly before death, when sepsis occurred as a complication. A Pel-Ebstein temperature curve was obtained during the entire period of hospitalization. This is rare in leukemia and is more frequently associated with Hodgkin's disease. There were temporary hemiparesis and motor aphasia, which lasted for one week, the cause of which could not be explained on postmortem examination.

Menometrorrhagia in Puberty. DR. BORIS B. RUBENSTEIN.

Menometrorrhagia may be defined as excessive bleeding at and between menstrual periods. Bleeding may occur from either an atrophic or a hyperplastic endometrium. The possibility of a blood dyscrasia or of the presence of polyps or other tumors must be ruled out. The mechanism of functional bleeding remains unknown. The objective of therapy is to reproduce the normal cyclic endometrial pattern and normal menstruation. The vaginal smear technic permits the determination, without invasion of the uterus, of the type of endometrium from which the bleeding occurs. A vaginal smear consisting almost wholly of basal epithelial cells indicates the presence of an atrophic endometrium. Therapy is therefore directed to stimulation of the endometrium with estrogen. Suggested dosage is diethylstilbestrol or α-estradiol dipropionate, 5 mg. per week until cessation of bleeding, after which the dose may be tapered off gradually.

In 4 patients so treated normal periodic bleeding occurred.

A vaginal smear consisting of cornified squamous epithelial cells suggests that the endometrium is probably hyperplastic. The therapy (to convert the endometrium to the secretory phase) is administration of adequate quantities of progesterone. In 2 patients so treated (receiving 10 mg. of progesterone per day for five days) bleeding stopped on the third day of therapy. Normal menstruation

began within forty-eight hours after interruption of therapy. Periodic bleeding has recurred for three months without further therapy.

Since the vaginal smear technic for this purpose is easy and acceptable to the patient, it provides a valuable guide for the choice of therapy in menometrorrhagia.

Calcinosis Circumscripta. DR. RALPH H. KUNSTADTER.

This 15 year old girl presents an unusual form of calcium deposition in childhood. The presence of healed childhood tuberculosis adds to difficulty in management, as attempts to decalcify the deposits may result in a breakdown of the healed tuberculous lesion.

Hard, painful nodules in and under the skin of the fingers were first noticed at the age of 10 years. During the last five years there has been a gradual increase in their number, with involvement of the toes and recently of the region of the left elbow. Except for pain and tenderness of the finger tips and toes over the pressure areas she has no complaints. Occasionally chalky material is expelled spontaneously from the finger tips.

Her developmental history is normal. She received no cod liver oil during infancy. Following measles and pertussis at the age of 6 years she acquired childhood tuberculosis. The family history shows no instances of a similar condition.

She is an unusually well developed and well nourished girl, who presents on physical examinations nothing unusual except irregular hard, stonelike areas over the fingers, toes and left elbow, involving the skin and subcutaneous tissue; some are tender. White, chalky material can be seen on the surface of the skin of the thumbs and index fingers and can be removed with a curet. Peripheral vascular studies show no abnormal changes.

The Mantoux test with a dilution of 1 : 1000 gave a 4 plus reaction. Renal and hepatic functions are normal. The p_H and the carbon dioxide content of the blood are normal. The uric acid content of the serum is 4.3 mg. per hundred cubic centimeters. Nine determinations of serum calcium over a period of four years gave results varying from 10.1 to 11.8 mg. per hundred cubic centimeters, with an average of 10.7 mg. Serum phosphorus levels varied from 3.5 to 4.9 mg. per hundred cubic centimeters with an average of 3.94 mg. for seven determinations. The amount of ionizable calcium varied from 4.3 to 5.3 mg. per hundred cubic centimeters. The serum phosphatase level was within normal limits. During balance studies, the calcium content of the serum was 10.8 mg. and the phosphorus content 3.7 mg. per hundred cubic centimeters, and the urinary excretion of calcium was slightly diminished. Biopsy showed hyperkeratosis, with deposits of calcium carbonate and calcium phosphate in the superficial epidermis and dermis.

Roentgenograms of the chest reveal calcification in the right hilus, indicative of healed childhood tuberculosis. The urinary tract, the skull and the long bones are normal. Roentgenograms of the extremities demonstrate calcium deposits in the skin and subcutaneous tissue in the regions of the fingers, toes and left elbow. There is no involvement of the tendons, muscles or viscera.

Attempts to decalcify the lesions have been disappointing. Spontaneous absorption has occurred in a localized form of the disease.

Book Reviews

Nephritis. By Leopold Lichtwitz, M.D. Price, $5.50. Pp. 344, with 120 illustrations and tables. New York: Grune & Stratton, Inc., 1942.

According to the author's preface this treatise on nephritis is written with "the basic conviction that clinical medicine is a science in its own right and not an appendix either to pathological anatomy or experimental physiology." However, the first nine chapters of a total of fourteen, comprising exactly two thirds of the book, are devoted to pathology and physiology. Much of this material is of a speculative and controversial nature and represents the author's own views and observations. It provides interesting reading for those especially interested in nephritis, but the busy practicing physician looking for practical assistance in the diagnosis and treatment of nephritis and nephrosis may not care to read that amount of material.

There are chapters on clinical physiology of the kidney, albuminuria, water metabolism, edema, estimation of renal function, renal acidosis, uremia, blood pressure and pathogenesis of nephritis. There is a good discussion of the theories and treatment of edema. The discussion of uremia may prove confusing to many, for the author regards the acute cerebral manifestations which often occur in acute nephritis as eclamptic or acute uremia. Many authorities do not consider this condition as uremia but prefer to designate it as "hypertensive encephalopathy" or "acute cerebral complications of nephritis." One chapter is devoted to an analysis of excretory capacity and of renal functions. The author claims simplicity for his methods and routine and a much more accurate estimation of the actual functioning state of the kidneys than is obtained by the usual tests of function. The latter may be true, but a routine which requires rest in bed for seven days, special diet, control and measurement of fluid intake and output and daily laboratory estimations of excreted chloride and nitrogen can hardly be considered less complicated than the ordinary tests of function.

The portion of the book devoted to clinical discussion includes chapters on acute diffuse glomerulonephritis, chronic diffuse glomerulonephritis, focal nephritis, nephrosis and renal disease in pregnancy. Of course there are practically as many classifications of nephritis as there are writers on the subject; so criticism of the classification is not made. However, there is question as to the status of focal nephritis as a separate clinical entity.

Some will undoubtedly disagree with many of the statements concerning prognosis, diagnosis and treatment of acute glomerulonephritis as applied to children. One phase of his treatment, complete starvation with no food or fluids for the first three to five days, is a rather drastic procedure for a child who is ill with an acute infection and often dehydrated; such a routine is not advised by pediatric writers on the subject. The discussion of nephrosis also contains statements open to question. For instance, in reference to lipid nephrosis in children the author states: "In the majority of cases the origin of the nephrosis can be traced to an infectious disease." Pediatric authorities on nephrosis do not agree with this observation.

Throughout the clinical chapters no distinction is made between nephritis and nephrosis in adults and in children, with a very few exceptions. Most writers follow this same plan. Pediatricians who have worked in this field recognize that the course and prognosis of these conditions in children may differ widely from their behavior in adults; also, tests used for estimation of function in adults may not be practicable for children.

In general, it may be said that the book will be interesting and stimulating to the worker in this field. However, it will not be of great benefit to the busy general pediatrician who is looking for practical ideas on diagnosis, treatment and prognosis of children's kidney diseases.

Textbook of Clinical Parasitology. By Clifford L. Belding, M.D. Price, $8.50. Pp. 890, with 1356 illustrations on 279 figures. New York: D. Appleton-Century Company, Inc., 1942.

The author's experience gleaned during years of teaching parasitology has been of invaluable aid in the preparation of this book. The organization of the text and the wealth of diagrams, drawings and summarizing tables bear witness to the years of effort that preceded the writing of this volume. The author has culled and edited pertinent literature from thousands of sources, including the most recent contributions in the field.

The first section of the book deals with the concepts of parasitology and serves to acquaint the novice with the fundamentals of this science. The last section is devoted to methods of diagnosis peculiar to parasitology and to drugs that have been shown to be valuable against parasitic infections and includes the complete technic of their uses.

The remainder of the book is devoted to discussions of the specific parasitisms of man. Each parasite is fully described, and then the author discusses the disease produced by it in man under the headings of pathogenesis, diagnosis, prognosis, treatment and prevention. The volume is comprehensive and includes a study of most of the animal parasites reported as infecting man.

One section is devoted to protozoan parasites and the diseases caused by them. Of particular interest in this category are amebiasis and malaria and the diseases associated with Giardia and Trichomonas infections.

Two fifths of the book is devoted to diseases caused by the helminth parasites. Of especial interest in this group are those helminths that recent investigations have shown to be more common than has heretofore been suspected, such as the trichina parasite and the pinworm. The most recent therapy of infections with commonly encountered parasites, such as Ascaris, the hookworm and the pinworms, is of great value.

The remainder of the book is given to discussions of the arthropod parasites. In addition to those with venenating properties and those that invade tissues, disease-transmitting agents are fully discussed.

It is the duty of every physician who may be called on for service in parts of the globe where he will encounter diseases foreign to the United States to acquaint himself with these exotic diseases. In this category are diseases of great importance in certain localities, such as the trypanosomiases, pork tapeworm infections, several diseases caused by flukes and diseases due to or transmitted by blood-sucking insects. Several serious tropical parasitisms, such as filariasis and schistosomiasis, may not be manifested for years after they are acquired, and a knowledge of their geographic distribution and their prevention is important.

In view of the need for more emphasis on parasitology in medical schools, this book is highly recommended for teaching purposes.

This book should be in every pediatrician's office. It is not generally realized that Giardia infection is common and may cause gastrointestinal complaints in children, that santonin and chenopodium have been superseded by less toxic and more effective remedies for helminthic diseases and that pinworm infection usually cannot be diagnosed by fecal examinations.

Chemistry and Physiology of the Vitamins. By H. R. Rosenberg, Sc.D. Price, $12.00. Pp. 674, with 25 illustrations. New York: Interscience Publishers, Inc., 1942.

This is a fine volume on the chemistry and physiology of the vitamins, which should be welcomed by all physicians interested in pediatrics as well as by those interested in other specialties. This up-to-date presentation fills a much needed gap. There is an extensive bibliography of special technical articles and monographs on the work in this field, which is now contained in a comprehensive review under one cover through the publication of this volume.

Dr. Rosenberg has adequately reviewed the general history, definition, nomenclature and isolation of the vitamins in the first 30 pages. Then with minute detail he reviews the knowledge to date of the chemistry and physiology of the specific vitamins. Included in these discussions are the chemical procedures for isolation of the vitamins, the proof of their chemical constituents and their synthesis and methods for determining the specific vitamins; these are divided into physical, chemical, biochemical and biologic methods. The plant and animal physiology is thoroughly discussed, and clinical tests and methods are given in detail. Dr. Rosenberg has combed the past and recent literature, and proper acknowledgment is given to each worker in the field for his contribution.

All vitamins are of importance to those interested in pediatrics, and Dr. Rosenberg has skilfully included the clinical significance of each in its place. Each vitamin has its function, and the physiology should not be overlooked even though the clinical application may not be clear at the present day. An appendix includes discussions concerning the "vitagens"; here the author takes up the essential fatty acids and amino acids, the essential carbohydrates, choline and related compounds and the essential organic sulfur-containing compounds.

There are a comprehensive patent index and an author and a subject index. The book is remarkedly well printed, well organized and exceptionally well indexed. The author and publisher are to be congratulated on the excellence of this book.

Your Children at School. By Elizabeth Vernon Hubbard. Price, not given. Pp. 176, with 25 illustrations. New York: The John Day Company, Inc., 1942.

This account of what goes on in a first grade is the next best thing to spending many hours as an observer in a schoolroom where the teacher is an artist who knows children. For the physician who cannot spare the time to see for himself, here is an unusual opportunity to read just what a teacher does with her children. From reports of the conversation and the behavior of 6 year old children in school, one learns how they feel, how they react to many kinds of situations and how they adjust and develop. One may assume that the educational methods fairly represent "progressive education" because one has the authority of the president of the Progressive Education Association, Carlton Washburne, for the statement: "Elizabeth Vernon Hubbard is one of the most artistic primary teachers I have ever known."

Fresh, first hand descriptions of activity, of creative expression and of individual guidance give a new understanding of the possibilities of a capable teacher in bringing about psychologic and social adjustment of children. Mrs. Hubbard's appreciation of individual differences of children will appeal to the clinically trained physician. Her case reports show planning, study of the home environment, shrewd observation and analysis and that right amount of "reasonable and competent authority" that gives the child a sense of security.

For all who try to understand and help the whole child, this is a significant and inspiring account of teaching in the first grade.

Nursing of Children. By Gladys Sellew, B.S., R.N., Ph.D. Price, $2.75. Pp. 579, with 53 illustrations. Philadelphia: W. B. Saunders Company, 1942.

The fact that the author has revised the original text four times since 1926 in itself speaks for her alertness in the field of child care. This edition bears a new title, the third since the original. It apparently has been influenced by the standards for nursing in the "Curriculum Guide for Schools of Nursing" and other authorities widely known among pediatricians.

The content is an expansion of the topics outlined in the unit division on the Nursing of Children. This serves considerably to introduce the reader to the present day thought of child care, which is in contrast to the former idea, in which the emphasis was on the need for knowledge of the physical care and the technic of procedure.

The illustrations vary little from those in the original edition, and so are not in keeping with the modern trend.

The questions and problems listed at the end of each chapter require a recall type of answer and memorizing of the chapter content, which may or may not help the nurse apply what she has learned in her contact with the well or sick child.

This textbook for student nurses succeeds in presenting a wide sampling of situations encountered in the nursing of infants and children. It is compact and will require application to individual children by supervisory guidance and classroom discussion.

Physical Diagnosis. By the late R. C. Cabot and F. D. Adams. Revised by F. Dennette Adams, M.D. Thirteenth edition. Price, $5.00. Pp. 888, with 399 illustrations. Baltimore: The Williams & Wilkins Company, 1942.

In the first eleven editions of this excellent text R. C. Cabot followed the plan of describing only those technics with which he had had personal experience and was guided by what he called "the personal equation" in the discussion of disease. In the twelfth edition Dr. Adams drew freely from the experiences of his colleagues at the Massachusetts General Hospital and greatly enlarged the scope of the book, adding discussions of clinical entities and illustrations from recent clinical material.

In this, the thirteenth edition, there has been included, besides new photographs, illustrations and roentgenologic prints, an excellent section on inadequate cardiac output due to (*a*) disturbance of the heart and (*b*) deficient volume of circulating blood (shock). The sections on the mouth, back, pulse, classification of heart murmurs and coronary heart disease have been thoroughly reorganized. The list of clinical entities discussed throughout the entire book has been increased.

The discussions of disease in this book are now so elaborate that it is no longer a text of physical diagnosis with evaluation of physical signs but rather a textbook of medicine with special reference to physical diagnosis.

The March of Medicine. Number VI of The New York Academy of Medicine Lectures to the Laity. Price, $2.00. Pp. 154, with 3 illustrations. New York: Columbia University Press, 1941.

This book should be on the waiting room table of every physician, but before it gets there the physician himself should have read it through. Sixth of a series of lectures to the laity sponsored by the New York Academy of Medicine, it represents an excellent approach of the values of scientific medicine to the problems of the individual.

The introduction, by Haven Emerson, M.D., "Humanism and Science," by Alan Gregg, M.D., and "Philosophy as Therapy," by Irwin Edman, Ph.D., are the outstanding lectures on the relationship between the physician and the patient. These should be required reading for every physician.

"Parcelsus in the Light of Four Hundred Years," by Henry E. Sigerist, M.D., "Psychiatry and the Normal Life," by William Healy, M.D., "The Promise of Endocrinology," by Oscar Riddle, Ph.D. and "What We Do Know About Cancer," by Francis Carter Wood, M.D., all cover their subjects well within the understanding of the lay reader.

The New York Academy of Medicine is to be congratulated on the quality of these lectures and deserves best wishes for the succeeding years.

Psychologic Care During Infancy and Childhood. By Drs. Ruth Morris Bakwin and Harry Bakwin. Price, $3.50. Pp. 331, with 31 illustrations. New York: D. Appleton-Century Company, Inc., 1942.

This is an excellent textbook for the physician on the problems of mental health. With short descriptions of the general principles underlying mental health as a background, the authors discuss briefly the common problems met in rearing children and indicate in a general way the best methods for meeting them.

A few of the subjects discussed are: Methods for general examination; intelligence tests and types of intellectual development; glandular disturbances; emo-

tional disturbances, their causes and treatment; habit formation, and care of the newborn. Since the book was written for the physician in general, exhaustive psychiatric studies and the more complicated methods of psychotherapy are not discussed. The book emphasizes the general causes of mental ill health and methods of treatment which can be carried out by any physician. In this way the authors are able to present the generally accepted pediatric and psychiatric viewpoints. The book having been written around symptoms of behavior, a clearcut picture of growth and development was not attempted by the authors.

This volume is well written, interesting and valuable for general reading and as a reference.

Seasonal Influence on Growth, Function and Inheritance. By Prof. A. B. Fitt. Price, 10s. 6d. Pp. 182, with 11 illustrations and 41 tables. Christchurch, New Zealand: Whitcombe & Tombs, Ltd., 1941.

The author, who is professor of education in Auckland University College (New Zealand), analyzes in this well written book a vast amount of material relative to the correlation between biologic functions and seasonal variations. He finds that with the exception of linear growth, biologic and constructive psychobiologic functions show a depression at the winter-spring or early spring season. Linear growth, however, is increased at this season. Also, emotional instability, as illustrated in the increase in crime, suicide and insanity, is at its height. He concludes that the human seasonal periodicity is of very complex origin, depending probably on an organic rhythm related to endocrine activity. This, in turn, may be influenced by external factors, one of the most important of which seems to be solar light.

Directory of Medical Specialists, 1942. Compiled by the Advisory Board for Medical Specialties. Price, $7.00. Pp. xvi + 2495, with no illustrations. New York: Columbia University Press, 1942.

This large volume, of 2,495 pages, is the up-to-date record of those who have passed the examinations of the various American boards for certifying medical specialists. In addition to the biographic data, there are contained statements regarding the organization of the Advisory Board and the rules of each separate board. Each set of rules is presented just before the list of specialists certified by that board. The increase in the size of the volume indicates the popularity of these boards and speaks well for the advances in medical education in the United States and neighboring countries.

Atresia congénita del esófago. By Alfredo U. Ramon-Guerra, Hector C. Bazzano and Juan F. Cassinelli. Price, not given. Pp. 34, with 14 figures. Montevideo: J. Garcia Morales, 1941.

Three cases of congenital atresia of the esophagus are presented with roentgenograms. In 2 of the cases, the diagnosis was confirmed by autopsy. While this is a rare congenital deformity, it is more frequent than statistics would indicate. It should always be considered in cases of asphyxia in the newborn with a bronchopneumonic syndrome. The condition is incompatible with life, and operation holds the only hope; but as yet the technic has not been successfully standardized.

Modern Bread from the Viewpoint of Nutrition. By Henry C. Sherman and Constance S. Pearson. Price, $1.75. Pp. 118, with no illustrations. New York: The Macmillan Company, 1942.

H. C. Sherman and C. S. Pearson present a valuable treatise on the new enriched breads. This book will appeal to all who are interested in nutrition. A detailed account is given of the improvements made in enriching breads with the essential food elements, proteins, minerals and vitamins. The authors conclude that bread may now be utilized to supply as much as 40 per cent of the calories in the normal diet without producing a deficiency in the necessary amounts of these essential food elements. An extensive bibliography is included.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, University of Michigan, Ann Arbor, Mich.

Canadian Committee:

Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Pediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14a, Utrecht.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p.m.

*Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialkstr., Tel Aviv.
Secretar: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Marique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Velado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico City.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico City.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Ernesto Vizcarrondo, Venezuela.
Secretary: Dr E. Santos Mendoza, Venezuela.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincare, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Conrado Pelfort, Ave 18 de Julio 1246, Montevideo.
Secretary: Dr. Héctor Mourigan, Ave 18 de Julio 2175, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.
Place: San Francisco.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Edward C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Palmer House, Chicago. Time: Nov. 4-7, 1942.
Region IV. Meeting cancelled.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Edwards A. Park, Johns Hopkins Hospital, Baltimore, Md.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. George M. Guest, Children's Hospital, Cincinnati.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 2:30 p. m.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. George M. Lyon, 955–4th Ave., Huntington, W. Va.
Secretary: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARIZONA PEDIATRIC SOCIETY

President: Dr. Vivian Tappan, San Clemente, Tucson.
Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. John J. Miller Jr., 2398 Sacramento St., San Francisco.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Ludo Von Meysenbug, Box 3356, Daytona Beach.
Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St., N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Ernest Caulfield, 683 Asylum Ave., Hartford.
Secretary: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

Louisiana State Pediatric Society

President: Dr. S. G. Wolfe, 1560 Line Ave., Shreveport.
Secretary-Treasurer: Dr. W. C. Rivenbark, 1448 Louisiana Ave., New Oleans.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J Orr, 135 Linwood Ave., Buffalo.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1942.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Secretary: Dr. Leon DeVel, 110 E. Fulton, Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. Andrew G. Dow, 314 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John M. Thomas, 301 N. 49th St., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Hampshire Pediatric Society

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Thomas M. Watson, Greenville.
Secretary: Dr. Frederick B. Haar, Greenville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas.
Secretary-Treasurer: Dr. John Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. David Zahn, 2474 Valentine Ave., New York.
Secretary: Dr. Harry J. Cohen, 975 Walton Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Paul L. Parrish, 52 S. Oxford St., Brooklyn.
Secretary: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Granada Hotel. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Buffalo Pediatric Society

President: Dr. A. Wilmot Jacobsen, 187 Bryant St., Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

Chicago Pediatric Society

President: Dr. James H. Wallace, 715 Lake St., Oak Park, Ill.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Cincinnati Pediatric Society

President: Dr. Lloyd K. Felter, 3144 Jefferson Ave., Cincinnati.
Secretary: Dr. Leo S. Friedman, 3586 Reading Rd., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Bruce A. Knickerbocker, 3403 Hall St., Dallas, Texas.
Secretary-Treasurer: Dr. Floyd A. Norman, 4325 Cole Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Hugh Lewis, Detroit, Mich.
Secretary: Dr. John J. Pollack, 622-26 Maccabees Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn. Houston. Time: Fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Edwin H. Schorer, 1103 Grand Ave., Kansas City.
Secretary: Dr. H. E. Petersen, Physicians and Surgeon's Bldg., St. Joseph, Mo.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Irwin Schiff, 658 Eastern Parkway, Brooklyn.
Secretary: Dr. Henry Rascoff, 895 Eastern Parkway, Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02–91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. James M. Moser, 3751 Jenifer St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William A, Howard, 2222 Que St. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

Memphis Pediatric Society

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. John H. Reynolds, 1628 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
Place: Milwaukee Athletic Club. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Alfred Langmann, 108 E. 68th St., New York.
Secretary: Dr. Edith M. Lincoln, 600 Park Ave., New York.
Place: New York Academy of Medicine, 2 E, 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Affiliates

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

Northwestern Pediatric Society

President: Dr. John M. Adams, 1009 Nicollet Ave., Minneapolis.
Secretary-Treasurer: Dr. Albert V. Stoesser, 205 W. University Hospital, Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

Philadelphia Pediatric Society

President: Dr. Paul B. Cassidy, 2037 Pine St., Philadelphia.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d. St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, 125 De Soto St., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.
Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Maurice J. Lonsway, 3720 Washington Blvd., St. Louis.
Secretary-Treasurer: Dr. Mary A. McLoon, 408 Humboldt Bldg., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

Seattle Pediatric Society

President: Dr. Frederick B. Joy, Stimson Bldg., Seattle.
Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Paul Hamilton, 1635 Chelsea Rd., San Marino, Calif.
Secretary: Dr. Helen Hopkins, 3875 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.